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ORIGINAL ARTICLE

Preparation and Evaluation of Lisinopril Tablet by Using Different Granulation Method

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ABSTRACT
The focal point of the ongoing review was the numerous strategies used to make strong measurement structures, like tablets, containers, and granules, among others. Consistency, smooth flow, and similarity are the advantageous characteristics of granules. Agglomeration is a cutting-edge granulation procedure utilised in the drug industry. Excipients that are suitable for the definition of measurement structures have been picked in light of their properties. The physiological parameters of bulk density, tapped density, hausner ratio, and compressibility index must be evaluated and optimised for effective pharmaceutical formulations. Notwithstanding physiological elements, evaluation models for finished products ought to consider factors like in-vitro discharge tests and breakdown time. Here, we're generally focusing on different granulation strategies.
Keywords: *Granulation, Tablets, Formulation, Excipients, Lisinopril*

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INTRODUCTION

Granulation, a method for increasing the size of particles through agglomeration, is one of the most important steps in the production of pharmaceutical dosage forms, particularly capsules and tablets. During the granulation process, smaller, coarser, or finer particles are transformed into larger, granule-shaped particles. Normally, granulation starts after first dry blending the necessary powder parts and the medication to guarantee an even circulation of every fixing through the powder mix. Molecule sizes of the granules utilised in the drug business range from 0.2 to 4.0 mm. They are first produced as a halfway with a size scope of 0.2 to 0.5 mm to either gather as a measurement structure or be mixed with other excipients preceding tablet compaction. The ideal granule qualities for tablet compaction incorporate a roundabout shape to increment the stream, a tight molecule size conveyance content consistency, enough fines to occupy void spaces between granules for better compaction and pressure qualities, hardness to forestall breaking, sufficient dampness, and insignificant residue development during the process. The API and excipients' particle sizes, the type, concentration, and volume of the binder and/or solvents, the granulation time, the type of granulator, the drying rate, and other factors influence the characteristics of the particles included after granulation. Particle design's ideal is granulation. Strong scaffolds, compound responses, sintering, the testimony of colloidal particles, and crystallisation are a portion of the underlying cycles used to make agglomerated granules. Moreover, restricting can be completed through glue and durable materials when high thickness covers are utilised. Wetting and nucleation, blend or development, combination, and steady loss or breakage are the few cycles by which granules are made from the powder particles. [2, 3]

Lisinopril:

Angiotensin-converting enzyme inhibitor lisinopril is a short-actingmedicine that has been approved to treat hypertension. 25–29% of the dose is absorbed when taken orally; Pharmacological efficacy does not

require biotransformation. The benefits begin to take effect one to two hours after consumption, and they last for 24 hours. The primary method of elimination is renal excretion, which has a reported half-life of 12.6 hours in normotensive individuals. A delayed half-life and development have been noted in people with poor renal capability (creatinine freedom of 30 ml/min). For the treatment of fundamental hypertension, studies have exhibited that lisinopril (20–80 mg/d) is similarly successful all around as hydrochlorothiazide, nifedipine, and beta-blockers. Moreover, it has proven successful in treating renovascular hypertension. Portions of 2.5–20 mg/d appear to have hemodynamic impacts like captopril in congestive cardiovascular breakdown (CHF). The most well-known antagonistic impacts, including rash and proteinuria, have been discombobulation and hacking, revealed in a few patients. Connections with diuretics, potassium supplements, and perhaps nonsteroidal mitigating specialists might happen. When used to treat CHF and fundamental hypertension, lisinopril seems to have comparative viability to other antihypertensive medications as well as captopril. Further examination is important to decide if lisinopril is more secure or productive than captopril or enalapril in treating hypertension or CHF. In contrast to captopril, which must be taken every 8 to 12 hours, and enalapril, which may need to be taken twice daily, lisinopril's prolonged duration of action allows for a single daily dose [45]

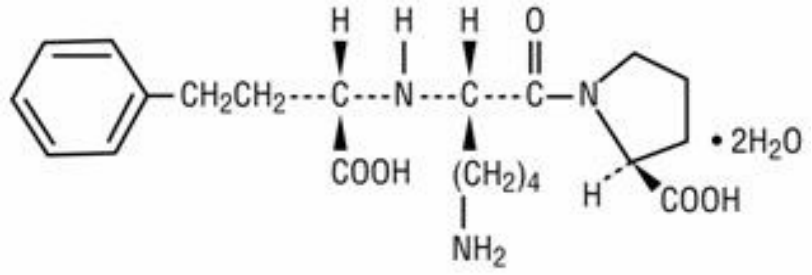

Figure no1: Structure of Lisinopril

Table no. 1: Formulation development of Lisinopril tab granulation Method

Chemical Name	(S)-1-(N2-(1-Carboxy-3-phenylpropyl)-L- lysyl)-L-proline
Category	Antihypertensive
Appearance	white to off-white, crystalline powder
Solubility	It is soluble in water, sparingly soluble in methanol, and practically Insoluble in ethanol.
Melting Point	Around 160˚C
Molecular Weight	441.52
Storage	Stored in air tight and light resistant container.

Mechanism of Action

It is believed that the major mechanism by which the medication lowers blood pressure is the inhibition of the renin-angiotensin-aldosterone pathway since lisinopril is antihypertensive even in patients with low-renin hypertension. In both humans and animals, lisinopril prevents the angiotensin-converting enzyme (ACE) from working. Angiotensin I is converted to angiotensin II, a chemical that constricts blood vessels, by the peptidyldipeptidase enzyme ACE. Aldosterone production by the adrenal cortex is also stimulated by angiotensin II. The renin-angiotensin-aldosterone pathway seems to be principally responsible for Lisinopril's favourable effects on hypertension and heart failure. Reduced plasma angiotensin II due to ACE inhibition also results in reduced vasopressor activity and aldosterone secretion [28]. A little rise in serum potassium may occur as a result of the latter drop. The mean rise in blood potassium was around 0.1 mEq/L in hypertensive individuals with normal renal function who were given Lisinopril alone for up to 24 weeks. [45]

MATERIAL AND METHODS

Drug candidate: Lisinopril was a gift from Watson Drugs in Hyderabad, while extra synthetic substances like PVP K30, Di-calcium phosphate, magnesium stearate powder, and crospovidone were totally purchased from Pallav Synthetic Substances and Vishal Synthetic Compounds in Mumbai. Lisinopril Tablet Arrangement Utilising Three Distinct Granulation Techniques Lisinopril tablets were made utilising three

distinct granulation methods. Three unmistakable granulation strategies utilising a punching machine were utilised to make the tablets after the fitting measures of prescription and excipients had been painstakingly gauged, joined, and gauged. 2.5 milligrams of lisinopril are remembered for every pill. [23, 24]

Table no. 2: Formulation development of Lisinopril tablet by different granulation Method

Ingredient	Wet Granulation Method			Dry GranulationMethod			Direct Compression Method		
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lisinopril	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Di-calcium phosphate	88.5	88.5	88.5	88.5	88.5	88.5	88.5	88.5	88.5
Polyvinylpyrrolidoe K 30	2%	4%	8%	2%	4%	8%	2%	4%	8%
Magnesium Stearate	03	03	03	03	03	03	03	03	03
Talc	03	03	03	03	03	03	03	03	03
Crospovidone	03	03	03	03	03	03	03	03	03

FORMULATION OF LISINOPRIL TABLET

Lisinopril tablet were created using three different methods: direct compression, dry granulation, and wet granulation. There are three distinct granulation techniques.

- **Direct compression**
- **Dry granulation**
- **Wet granulation**

With fixations going from 2% to 8%, fifteen details were made using different granulation methods for every one of the three definitions (2, 4, and 8). To ensure full blending, everything being equal, an exactly gauged amount of prescription, fasteners, and disintegrants is put into a glass mortar and ground completely. The other excipients, for example, dicalcium phosphate, magnesium stearate, and powder, are then included as a request and blended well. The powder is next analysed for characteristics connected with the stream. [23, 24]

Angle of repose

Using the pipe strategy, the point of rest is determined. A channel is utilised to take the definitively weighed combination. The channel is situated to such an extent that the tip simply contacts the highest point of the blend stack upon being raised to the appropriate level. On the outer layer of a piece of paper, the prescription and excipient combination are permitted to stream down the channel openly. The powder cone's distance across is estimated, and the point of rest is resolved utilising the condition underneath. [25]

$$\text{Tan } \theta = h/r$$

Where,

h = height of the cone r = radius of the cone θ = the angle of repose,

Table no. 3: Angle of Repose Flow Types

SL.NO	ANGLE OF REPOSE(θ)	TYPE OF FLOW
1	< 20	Excellent
2	20-30	Good
3	30-40	Passable
4	>40	Very poor

Procedure: A proper level pipe was utilised to pour estimated measures of powder (blend mix) onto the diagram paper. An estimate was made of the pile's level. Pencil marks were made around the store's border. The size of the all shapes and sizes of squares that made up the circle were utilised to process the region of the circle, and the boundary "r" not set in stone from the circle's region was utilised to ascertain the point of rest. [25]

Bulk density

Pouring a gauged amount of the blend into a graduated chamber and gauging and estimating the volume yields the clear mass thickness. [23]

$$\text{Bulk Density} = \frac{\text{Weight of the powder}}{\text{Volume of packing}}$$

Tapped Density

A graduated chamber with a known mass of the prescription and excipient blend is set inside to learn the tapping thickness. The chamber is tapped on a level surface at intervals of seconds from a level of 10 cm. The tapping is rehashed until there is, as of now, no tumultuous change. [23]

$$\text{Tapped density} = \frac{\text{Weight of the powder}}{\text{Tapped volume}}$$

Compressibility Index

As per Carr's compressibility file, the mix's compressibility record is determined. [23]

$$\text{Carr's compressibility index} = \frac{\text{Tapped density-bulk density}}{\text{Tapped density}} \times 100$$

Table no. 4: Carr's Index Properties

SL NO	% COMPRESSIBILITY INDEX	PROPERTIES
1	5-12	Free flowing
2	12-16	Good
3	18-21	Fair
4	23-35	Poor
5	33-38	Very poor
6	>40	Extremely poor

Hausner's ratio

The accompanying equation is utilized to work out Hausner's proportion: [23]

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Table no. 5: Hausner's ratio Property

SL.NO	HAUSNER'S RATIO	PROPERTY
1	0-1.2	Free flowing
2	**1.2-1.6**	**Cohesive flowing**

POST COMPRESSION EVALUATION

Hardness

By estimating how much power is expected to break a tablet transversely, the hardness of the tablet might be utilised to determine its solidarity. For uncoated tablets, it is considered adequate to have a hardness somewhere in the range of 3 and 5 kg/cm2. Utilising a Mansanto hardness analyzer, the hardness of 10 tablets from every plan was assessed. [13]

Thickness

By estimating how much power is expected to break a tablet transversely, the hardness of the tablet might be utilised to determine its solidarity. For uncoated tablets, it is considered adequate to have a hardness somewhere in the range of 3 and 5 kg/cm2. Utilising a Mansanto hardness analyzer, the hardness of 10 tablets from every plan was assessed. [13]

Diameter

Vernier calipers are used to measure the tablets' diameter. [23]

Drug content

Five pills from each cluster are gauged and ground; 10 mg of the powder is then taken and blended in with 10 ml of refined water to make 100 ml. From this, 10 ml of the arrangement is gathered, and 100 ml of refined water is added to the combination. Utilising an UV Spectrophotometer, the arrangement's still up in the air at 209 nm. [17]

Weight variation test

The typical load of one tablet is determined from the aggregate load of the twenty tablets after their individual and joined loads have been laid out utilising a mechanised weighing scale. [17] USP specification for the uniformity of weight.

Table no. 6: Weight Variation Differences

Sr. NO.	AVERAGE WEIGHT (mg)	MAXIMUM % DIFFERENCEALLOWED
1	130 or less	10%
2	130-324 mg	7.5%
3	More than 324 mg	5%

Friability test

Friability is the deficiency of tablet weight in the compartment because of surface-molecule evacuation. A friability test is performed to determine the tablet's protection from scraped spots during taking care of, pressing, and transportation. Tablet friability is resolved using the Roche friabilator. The friability of tablets is resolved by utilising 20 tablets from every plan. The pills are gauged prior to being placed into the Roche friabilator. 4 minutes are spent turning it at 25 rpm. The pills are powdered, then, at that point, rechecked. Utilising the technique again, the level of weight is not entirely set in stone. [17]

$$\text{Percentage friability} = \frac{\text{Initial weight- final weight}}{\text{Initial weight}} \times 100$$

Drug content uniformity:

Each bunch of 10 pills was gauged, and the typical is still up in the air. All pills were broken into powder, which was then disintegrated in phosphate cushion 6.8 to give an 80 mg portion, and the sum was then expanded to 100 ml. One millilitre of the stock arrangement was obtained, and 10 millilitres of phosphate cradles with a pH of 6.8 were utilised to make the volume. A sifted arrangement was utilised as a clear for spectrophotometrics. [17]

Disintegration test

A USP crumbling gadget and refined water are utilised for the breaking down test, which is completed at 27 0.5°C. The normal expressed opportunity to accomplish the full deterioration of six pills is recorded. [23]

Dissolution Studies

Utilising a USP type 2 (Oar) at 50 rpm, PBS 7.4 (pH) for 2 hours, and a temperature of 370.50 C, the delivery pace of the pre-arranged lisinopril is still up in the air. A 5 ml sample was taken out and supplanted with a similar volume of new medium at foreordained stretches. The eliminated tests were weakened with pH 7.4, separated, and afterward inspected using pH 7.4 as a clear on an UV spectrophotometer at 258 nm. The total medication discharge rate was calculated. [23]

Table no. 7: Dissolution Apparatus Specification.

Dissolution test apparatus	USP type II
Speed	50 rpm
Stirrer	Paddle type
Volume of medium	500 ml
Volume withdrawn	5 ml
Medium used	PBS-7.4(pH)
Temperature	37±0.5ºC

RESULTS AND DISCUSSION

Preliminary characterization: Identification of drug:

Organoleptic qualities, like tone, scent, taste, appearance, and dissolving point, were analysed in drug tests. The aftereffects of the got test's organoleptic attributes and liquefying are not entirely settled to be equivalent to those in the writing.

Table no. 8: Preliminary characterization of Lisinopril

Sr No.	Parameters	Reported Standard	Observed Result
1	Color	White	White
2	Odour	Odourless	Odourless
3	Taste	Bitter	Bitter
4	Appearance	Crystalline	Crystalline
5	Melting Point	160 ºC	158-159ºC

Table no. 9: Solubility data of drug in different solvent

Solvent	Observed resultsat
Distilled water	Freely soluble
Ethanol	Practically Insoluble
PBS-7.4(pH)	Freely soluble

U.V. Spectrophotometric analysis: Construction of calibration curve

10mg of unequivocally estimated lisinopril was weakened in 100 ml of 7.4 pH cushion solution to make a 100 mcg/ml stock arrangement. Aliquots of 10, 20, 30, 40, and 50 ml from the previously mentioned stock arrangement were pipetted into a progression of 100 ml volumetric carafes, and the volume was then raised to 100 ml to give a fixation going from 10 to 50 mcg/ml. Following that, the absorbance of the resultant arrangement was surveyed at 258 nm utilising an UV spectrophotometer with the comparing guardian dissolvable as a clear. By charting absorbance versus focus in mcg/ml, the standard bend was made.

Table no. 10: Absorbance concentration data for standard curves of Lisinopril in different solvents

Concentration (µg/ml)	PBS-7.4(pH) λmax - 258 nm
10	0.220
20	0.433
30	0.617
40	0.789
50	0.980

Table no. 11: Regression equation, Correlation coefficient and λMax of formulation

Media	Regression equation	Correlation coefficient	λMax nm
PBS-7.4(pH)	Y=0.0178x-0.066	0.9939	258nm

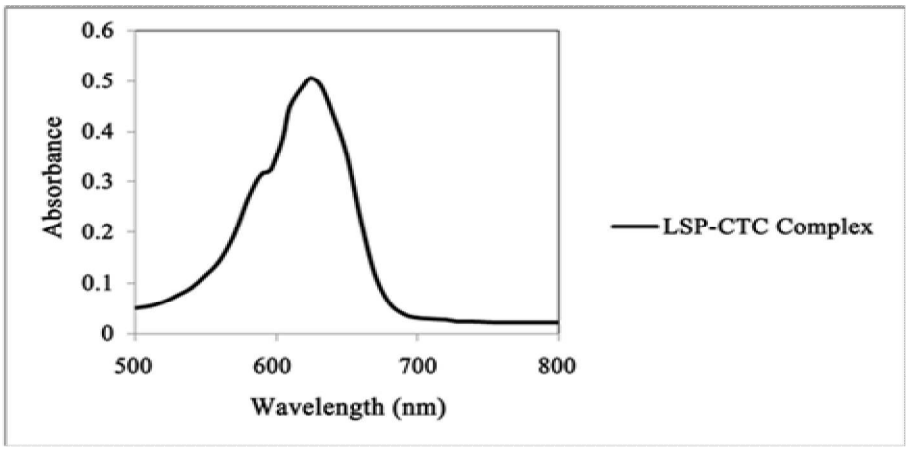

Figure 2: Curve in PBS-7.4(pH). λmax- 258nm Calibration curve of Lisinopril

FTIR Spectrum of Lisinopril: The medication test was inspected using a JASCO 4600 Administrator to do Fourier-Change Infrared Spectroscopy (FTIR). Wave numbers somewhere in the range of 4000 and 450 cm1 were utilised to check the range.

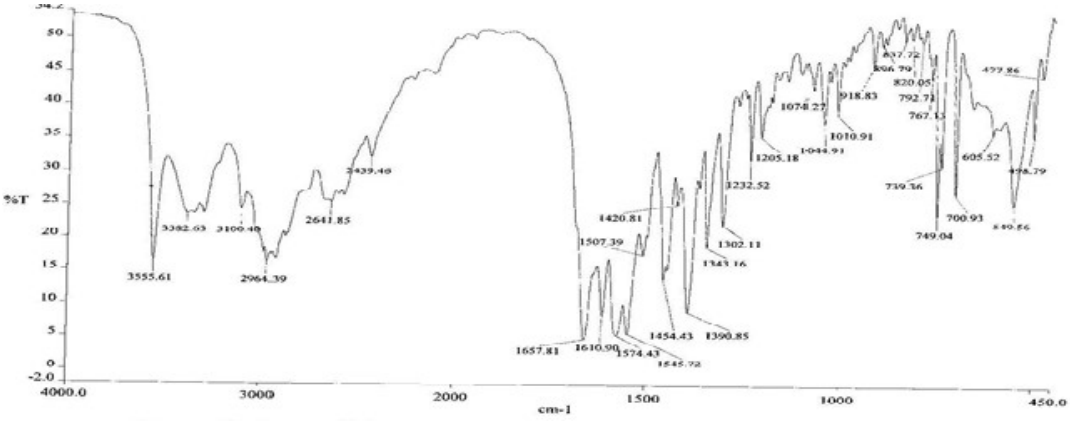

Figure 3: Calibration curve of Lisinopril

FORMULATION OF LISINOPRIL TABLET BY USING DIFFERENT GRANULATIONMETHOD:

Every plan's independently weighted powder blends were squashed into tablets utilising a single punch tablet packing machine. Every plan had fifty pills. The pills were circular and white for all intents and purposes. the components of every definition's tablet measurement.

Table no. 12: Formulation table of Lisinopril tablet

Ingredient	Wet Granulation Method			Dry GranulationMethod			Direct Compression Method		
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lisinopril	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Di-calcium phosphate	88.5	88.5	88.5	88.5	88.5	88.5	88.5	88.5	88.5
Polyvinyl pyrrolidone K 30	2%	4%	8%	2%	4%	8%	2%	4%	8%
Magnesium Stearate	03	03	03	03	03	03	03	03	03
Talc	03	03	03	03	03	03	03	03	03
Crospovidone	03	03	03	03	03	03	03	03	03

PRECOMPRESSION EVALUATIONS FOR THE POWDER BLEND

To ensure the powder mix's stream attributes were there, pre-pressure studies were conducted. The powder combination's great stream attributes will deliver tablets of important quality and make the tableting system more straightforward. Thusly, it was fundamental to assess the mix's ability to stream before applying pressure. The accompanying rundown addresses the different pre-pressure appraisals.

Angle of repose
Bulk density
Tapped density
Compressibility Index
Hausner's ratio

Formulations Number	Bulk Density (gm/cc)	Tapped Density (gm/cc)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (θ)
	DRY GRANULATION				
F1	0.3716±0.0010	4101±0.00257	7.27±0.637	1.177±0.0032	27.25±0.47
F2	0.3716±0.0012	4101±0.00256	7.27±0.623	1.177±0.0046	26.56±0.66
F3	0.3716±0.0013	4101±0.00254	7.27±0.636	1.177±0.0056	28.27±0.47
	WET GRANULATION				
F1	0.3716±0.0013	4101±0.00257	7.27±0.598	1.177±0.0076	29.77±0.51
F2	0.3716±0.0010	4101±0.0023	7.27±0.628	1.177±0.0073	30.52±0.72
F3	0.3716±0.0012	4101±0.0020	7.27±0.639	1.177±0.0071	31.07±0.90
	DIRECT COMPRESSION				
F1	0.3716±0.0011	4101±0.0023	7.27±0.654	1.177±0.0087	26.46±0.52
F2	0.3716±0.0008	4101±0.0028	7.27±0.644	1.177±0.0068	28.87±0.40
F3	0.3716±0.0010	4101±0.0027	7.27±0.687	1.177±0.0078	27.05±0.41

Table no. 13: Post Granulation Evaluation of Powder

POST COMPRESSION EVALUATIONS:

After pressure, the tablets were gathered, and they went through a few assessments to lay out their quality and ensure the completed item followed all pertinent prerequisites for tablets.

Hardness	Thickness
Diameter	Drug content
Weight variation	Friability test
Disintegration time	Dissolution test

Table no. 14: Physico-Chemical Characterization of Lisinopril Table

F. Code	Thickness (mm)*	Hardness (kg/cm2)*	Friability (%)	Weight Variation (m)	Drug content (%w/w)**	Disintegration Time
	Wet granulation					
F1	3.44±0.02	7.32±0.05	0.679±0.01	398.25±.139	97.83±0.69	02.35 min.
F2	3.37±0.06	7.65±0.01	0.503±0.04	397.25±2.39	99.59±1.05	02.88 min.
F3	3.40±0.09	7.75±0.03	0.417±0.02	397.65±1.94	98.95±0.87	02.35 min.
	Dry granulation					
F1	3.38±0.07	8.46±0.01	0.568±0.06	395.05±1.75	99.72±0.87	02.45 min.
F2	3.54±0.02	8.54±0.03	0.515±0.03	397.05±1.94	98.65±0.66	02.90 min.
F3	3.27±0.06	8.74±0.02	0.667±0.03	396.75±2.04	99.61±0.65	02.45 min.
	Direct compression					
F1	3.60±0.06	6.36±0.01	0.655±0.02	396.55±1.75	98.86±1.55	02.88 min.
F2	3.27±0.05	6.74±0.01	0.601±0.01	398.09±1.94	97.55±0.42	03.98 min.
F3	3.32±0.06	6.85±0.03	0.414±0.02	398.55±2.04	99.98±0.63	04.35 min.

*All the values are expressed as mean± SD, n=3

Dissolution test:

Medium: 0.1N HCL for 2hr, 500ml

Apparatus: Type I, 50 rpm

Table no. 15: % of Drug Release

Time in Min.	F1% CDR	F2% CDR	F3% CDR	F4% CDR	F5% CDR	F6% CDR	F7% CDR	F8% CDR	F9% CDR
15	48.08	32.57	31.76	33.47	39.36	35.37	64.53	55.33	53.46
30	60.29	41.09	42.69	44.43	49.32	43.78	71.84	68.04	67.88
60	74.54	51.17	53	56.7	55.96	69.08	78.56	73.81	71.45
90	85.21	68.23	62.81	66.06	67	69.96	92.8	84.43	80.64
120	92.6	85.9	83.8	80.6	91.03	85.5	99.78	92.6	90.45

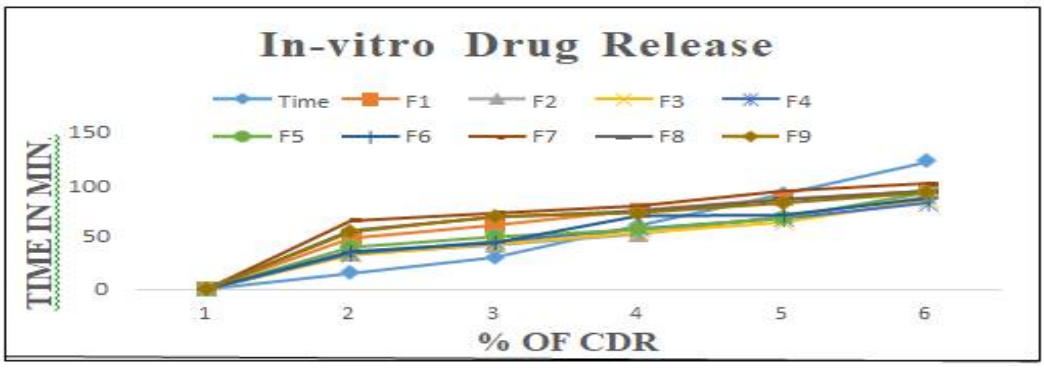

Figure 5: Dissolution Study of Batch F1-F9

Release kinetic studies:

To determine the energy of medication discharge, the in-vitro drug discharge information of all plans was broken down. First request energy, zero request energy, and the Higuchi model were undeniably used to match the information that had been assembled. The best connection coefficient (r2) found utilising these techniques gives insight into the model that fits the delivery information the best. The investigation of the connection coefficient r uncovered that the medication discharge followed the first request for discharge energy in view of the discoveries of motor examinations. It was found that the worth of r for the main request went between 0.981-0.992, which is near 1, contrasted with the Higuchi square root scope of

0.892-0.958 and the zero request scope of 0.895-0.969. Thus, it was accepted that it was following the principal request for discharge design that all plans followed. Moreover, the information was fitted into the dramatic Mt/Mama = Ktn model by Korsmeyer Peppa to fathom the medication discharge process. Where Mt/Mama addresses the level of the medication delivered after time , „k" the active steady, and „n is the delivery example that portrays the medication transport component. Somewhere in the range of 0.48 and 0.7911 is the scope of the delivery type (n). The qualities for "n" for the plans from F1 through F9 were all over 0.89, demonstrating that every one of the definitions utilised a non-fickian discharge instrument. The overall intricacy of the created details might be an indication that dissemination and disintegration together may have been controlling the medication discharge system.

Table no. 15: Release exponent values and release rate constant values for different formulations

Batch	Zero order	First order	Higuchi's plots	Korsmeyer-Peppas plots		Best fit Model	Drug release Mechanism
	R^2	R^2	R^2	R^2	Slope(N)		
F1	0.9293	0.982	0.9116	0.912	0.597	First order	Non-Fickian
F2	0.969	0.974	0.8944	0.915	0.594	First order	Non-Fickian
F3	0.916	0.984	0.9217	0.899	0.6077	First order	Non-Fickian
F4	0.946	0.978	0.8926	0.892	0.577	First order	Non-Fickian
F5	0.944	0.992	0.9581	0.902	0.488	First order	Non-Fickian
F6	0.896	0.958	0.9022	0.938	0.7911	First order	Non-Fickian
F7	0.896	0.981	0.9258	0.938	0.4838	First order	Non-Fickian

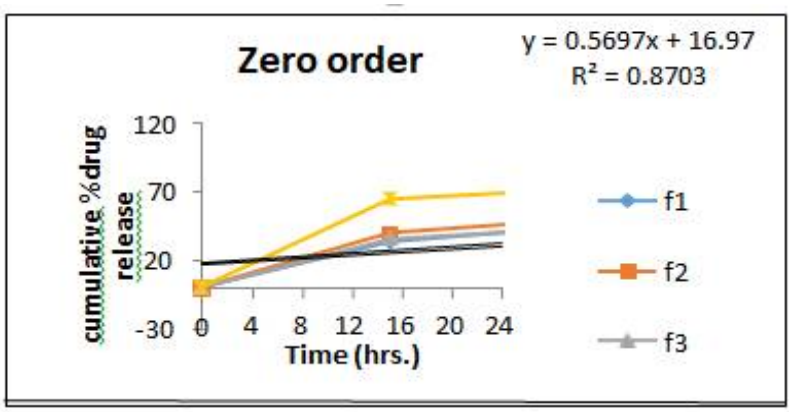

Figure 6: Zero order Model Drug Release Mechanism of F1-F4 Batch

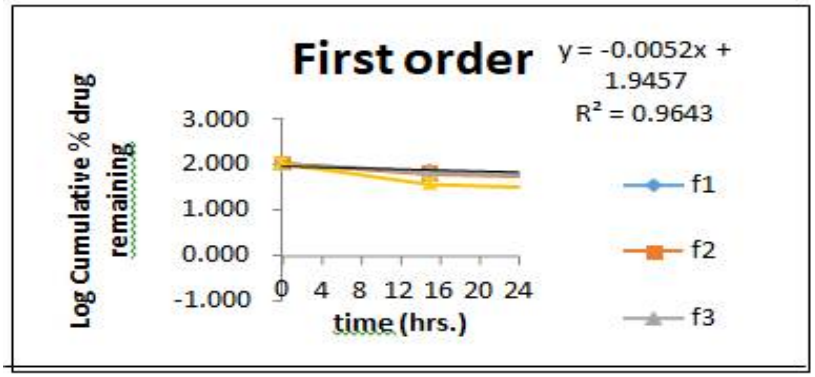

Figure 7: First order Model Drug Release Mechanism of F1-F4 Batch

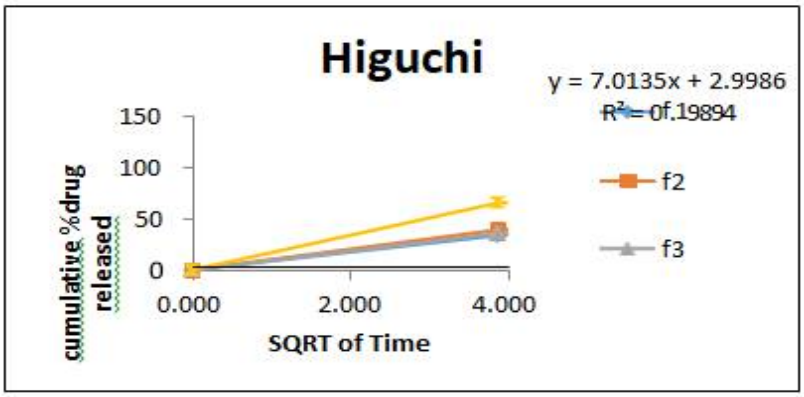

Figure 8: Higuchi Model Drug Release Mechanism of F1-F4 Batch

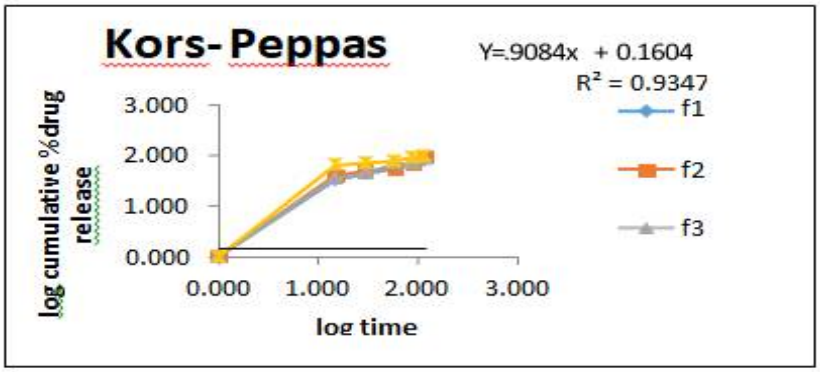

Figure 9: Kros-Peppas Model Drug Release Mechanism of F1-F4 Batch

CONCLUSION

The objective of the ongoing review was to plan and make lisinopril tablets using DCP, magnesium stearate, PVP K30, and powder. Because of its inescapable utilisation as an antihypertensive, it has been decided to create doses utilising a few granulation strategies.A decent plan ought to deliver its substance over a fair timeframe in a defined profile while utilising different granulation procedures and folio focuses. Lisinopril, a drug with a dynamic part, was surveyed for its actual properties, scientific profiles, and medication polymer similarity studies. The granules were made utilising three unique procedures: wet granulation, dry granulation, and direct pressure. Point of rest, mass thickness, tapped thickness, and Carr's list were completely tried for the pre-arranged granules. Not entirely settled to be great and inside as far as possible.

CONFLICT OF INTREST

There are no conflict of interest and disclosures regarding the work.

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