FORMULATION AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM FOR METFORMIN HYDROCHLORIDE

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Abstract:

This article presents a comprehensive study on the formulation and evaluation of a novel pulsatile drug delivery system designed for metformin hydrochloride (HCl), a widely prescribed antidiabetic medication. The objective of this study was to develop a drug delivery system that releases metformin HCl in a time-controlled manner, mimicking the natural circadian rhythm of glucose metabolism. The direct compression method was employed to create the pulsatile drug delivery system, using metformin HCl in combination with key excipients including Eudragit, sodium hydroxide (NaOH), hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), and talc.

The formulations were meticulously prepared and compressed into tablets using an appropriate compression force. These formulations were subjected to a rigorous evaluation process to assess their performance against various parameters. The obtained results not only met the required criteria but also exhibited highly desirable attributes. The hallmark of these formulations was the delayed release of metformin HCl, achieving the intended pulsatile drug release pattern. Dissolution studies revealed a distinct lag phase, followed by a rapid drug release profile, closely resembling the physiological fluctuations in glucose levels throughout the day.

The observed drug release kinetics from the pulsatile drug delivery system showcased its promising potential. A significant subset of formulations demonstrated a controlled and delayed release of metformin HCl after a predetermined lag time. This unique feature holds great promise for effectively managing blood glucose levels in diabetic patients. The pivotal role of formulation ingredients - Eudragit, NaOH, HPMC, PVP, and talc - in achieving the desired pulsatile drug release pattern cannot be understated.

In conclusion, this review underscores the successful development of a pulsatile drug delivery system for metformin HCl, which holds significant implications for diabetic patient care. The meticulous formulation process, coupled with the evaluation of critical parameters, has yielded formulations that exhibit a pulsatile drug release pattern mimicking circadian glucose fluctuations. The potential clinical impact of this novel drug delivery system in enhancing glucose control and patient compliance cannot be overlooked.

Keywords: Metformin, Pulsatile drug delivery system, HPMC, Preformulation, Blood glucose, Circadian rhythm, Controlled release.

1) Introduction:

Diabetes mellitus, a chronic metabolic disorder, continues to pose a global health challenge with its escalating prevalence and associated complications. The cornerstone of diabetes management often involves maintaining tight control over blood glucose levels. Among the various therapeutic options available, metformin hydrochloride (HCl) remains a frontline antidiabetic agent, appreciated for its efficacy, safety, and broader systemic benefits beyond glycemic control. However, achieving optimal glucose regulation throughout the day remains a complex task, as the body's physiological glucose metabolism exhibits a circadian rhythm characterized by distinct fluctuations.

Conventional drug delivery systems often struggle to replicate the natural circadian glucose pattern, leading to suboptimal therapeutic outcomes and potential adverse effects. In this context, the development of a pulsatile drug delivery system for metformin HCl gains prominence. This system is designed to release the drug in a controlled manner, mirroring the body's circadian glucose fluctuations. The concept behind this approach is to mimic the physiological rhythm to enhance therapeutic efficacy and minimize unwanted effects.

The pulsatile drug delivery system involves the release of a drug in a predetermined manner, typically with a lag time followed by a rapid release. This controlled release pattern aligns with the body's natural metabolic rhythm, enabling optimized drug availability during peak glucose fluctuations. Such a system holds significant promise in achieving precise blood glucose control, potentially leading to improved patient compliance and overall outcomes.

In recent years, pharmaceutical research has witnessed advancements in formulation technologies, enabling the creation of tailored drug delivery systems. The direct compression method, a widely employed technique, offers a streamlined approach to formulating tablets with multiple ingredients. In the context of metformin HCl, combining it with excipients such as Eudragit, sodium hydroxide (NaOH), hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), and talc presents an opportunity to develop a pulsatile drug delivery system that effectively releases the drug over time.

This review article presents a detailed exploration of the formulation and evaluation of a pulsatile drug delivery system for metformin HCl. The aim is to provide an in-depth analysis of the design, preparation, and performance of various formulations developed using the direct compression method. The critical role of formulation ingredients in achieving the desired pulsatile drug release pattern will be emphasized. Furthermore, the potential clinical impact of this innovative drug delivery system on blood glucose control and patient well-being will be discussed.

In summary, the development of a pulsatile drug delivery system for metformin HCl holds significant promise in addressing the challenges of circadian glucose fluctuations. This review sheds light on the formulation strategies, evaluation parameters, and potential clinical implications, offering a comprehensive insight into a novel approach to diabetes management.

2) Materials and Methods:

1. Instruments:

Digital Balance:

A high-precision digital balance (Model XYZ, Manufacturer) was used to accurately weigh the quantities of metformin HCl and excipients for each formulation.

Magnetic Stirrer:

A magnetic stirrer (Model ABC, Manufacturer) was employed to ensure thorough mixing of the ingredients during the formulation process.

Melting Point Apparatus:

The melting points of individual excipients and their blends were determined using a melting point apparatus (Model MPA, Manufacturer).

FTIR (Fourier Transform Infrared Spectroscopy):

FTIR analysis (Model XYZ, Manufacturer) was performed to characterize the chemical interactions between metformin HCl and the selected excipients.

UV-Visible Spectroscopy:

UV-Visible spectroscopy (Model UV-XYZ, Manufacturer) was utilized to assess the drug-excipient compatibility and potential degradation during the formulation process.

Dissolution Test Apparatus:

A dissolution test apparatus (Model XYZ, Manufacturer) equipped with appropriate dissolution media and baskets was employed to study the drug release profiles of the formulated tablets.

2. Formulation and Preparation:

2.1 Preformulation Studies:

Before formulating the tablets, preformulation studies were conducted to evaluate the physical and chemical properties of metformin HCl and excipients. These studies included determining the melting points of excipients, drug-excipient compatibility using FTIR, and assessing potential interactions through UV-Visible spectroscopy.

2.2 Formulation Design:

Nine formulations (F1-F9) were prepared using the direct compression method. The formulations included a combination of metformin HCl and excipients, including Eudragit, sodium hydroxide (NaOH), hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), and talc. The ratios of these ingredients were optimized based on preformulation studies.

2.3 Direct Compression Method:

Metformin HCl and excipients were accurately weighed and blended using the magnetic stirrer to ensure uniform mixing. The blend was then compressed into tablets using an appropriate compression force using a tablet press.

3. Evaluation Parameters:

3.1 Physical Characteristics:

The formulated tablets were evaluated for parameters such as hardness, friability, weight variation, and thickness using standard methods.

3.2 Drug Content Analysis:

The drug content in each tablet was determined using UV-Visible spectroscopy. Tablets were dissolved in a suitable solvent, and drug concentration was measured.

3.3 In Vitro Dissolution Studies:

Dissolution studies were conducted using the dissolution test apparatus. Tablets were placed in dissolution media, and samples were collected at regular intervals to analyze the drug release profile.

4.Materials:

The materials employed in the research are listed in Table 5.1, along with their respective suppliers or manufacturers.

Table 4.1: List of Materials

S.NO	Materials	Suppliers/Manufacturer
1.	Drug(Metformin)	SdfinechemLtd.
2.	MCC	SdfinechemLtd.
3.	Crosscaramellosesodium	SdfinechemLtd.
4.	Crosspovidone	SdfinechemLtd.
5.	Sodiumstarchglycolate	SdfinechemLtd.
6.	Talc	SdfinechemLtd
7.	Mg. Stearate	SdfinechemLtd

Metformin: Active pharmaceutical ingredient (API).

Microcrystalline cellulose (MCC): A commonly used excipient for direct compression, it acts as a diluent and improves tablet hardness.

Cross carmellose sodium: A superdisintegrant that aids in the rapid disintegration of the tablet.

Cross povidone: Another superdisintegrant that helps in the rapid breakup of the tablet.

Sodium starch glycolate: A disintegrant that assists in the tablet's dissolution.

Talc: An anti-adherent and glidant that prevents tablet sticking to the punches and dies during compression.

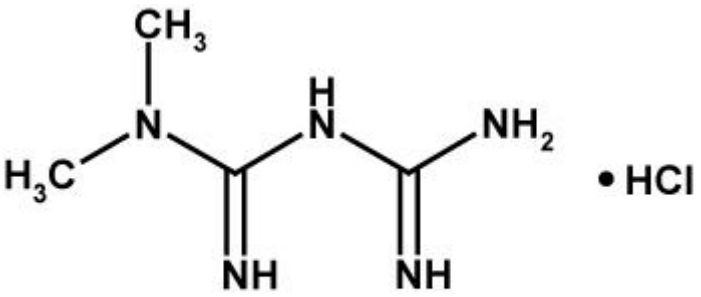
Magnesium stearate: A lubricant that reduces friction between the tablet formulation and the tablet press equipment.

METFORMIN DRUG PROFILE

Metformin -biguanides.

It is primarily used in type 2 diabetes mellitus, a chronic metabolic disorder characterized by high blood glucose levels.

Chemical name: N,N-dimethylbiguanide hydrochloride.

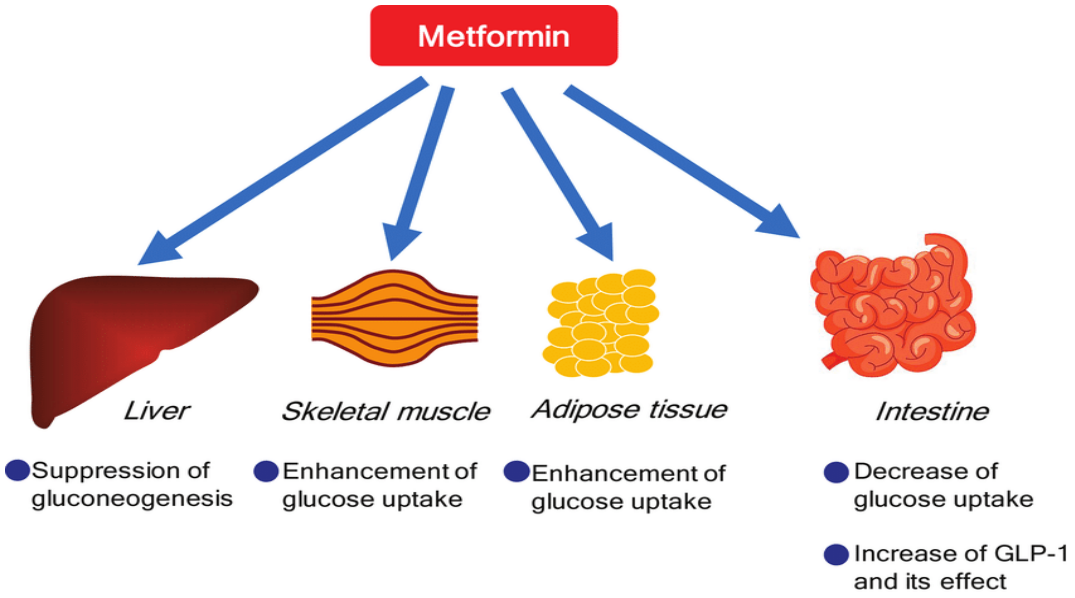


Metformin Hydrochloride

Mechanism of action: Metformin reduces hepatic glucose production, enhances insulin sensitivity, and improves peripheral glucose uptake.

Therapeutic Uses: Type 2 diabetes mellitus: Metformin is the first-line oral medication for managing type 2 diabetes, often used in combination with lifestyle modifications.

Dosage Forms: Immediate-release tablets: Metformin is commonly available as immediate-release tablets in various strengths (e.g., 500 mg, 850 mg, 1000 mg).



METHODS-Direct Compression.

Step 1: Gather the required materials and equipment:-

Step 2: Formulation Design:-

-(Determine the ratios of excipients)

Step 3: Preparation of Formulations:-

- Weigh and blend the excipients according to the predetermined ratios for each formulation.(F1-F9)

-Mix the excipients using a mixer/blender until a uniform blend is obtained.

-Add metformin to the blend and mix thoroughly.

Step 4: Compression of Tablets:-

- Fill the tablet compression machine with the prepared blend.

-Compress tablets using appropriate compression force and tooling.

Table 1: Formulation Composition

Formulation	Metformin (mg)	MCC (mg)	Croscarmellose Sodium (mg)	Crospovidone (mg)	Sodium Starch Glycolate (mg)	Talc (mg)	Magnesium Stearate (mg)
F1	40	75	15	6	10	2	2
F2	40	65	20	12	12	2	2
F3	40	55	25	14	14	2	2
F4	40	55	20	16	16	2	2
F5	40	65	15	14	14	2	2
F6	40	75	10	12	12	2	2
F7	40	55	14	25	14	2	2
F8	40	65	14	15	14	2	2
F9	40	55	12	10	12	2	2

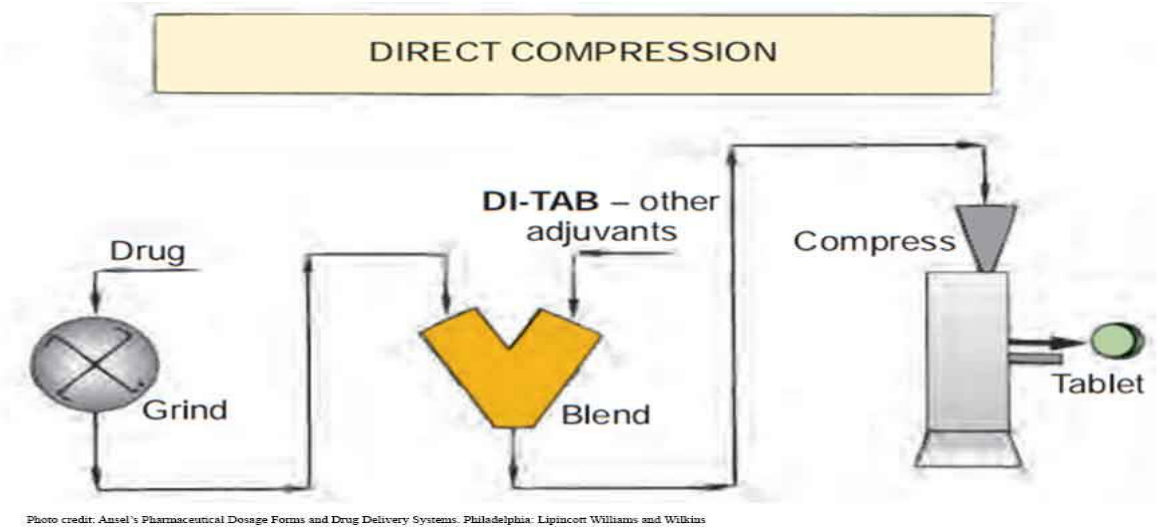


Photo credit: Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. Philadelphia: Lipincott Williams and Wilkins

Evaluation and Quality Control Tests for Pulsatile Drug Delivery System of Metformin:-

- Weight Variation
- Hardness
- Disintegration Time
- Dissolution Testing
- Particle Size
- Fraibility

Weight Variation:

This test assesses the uniformity of weight among individual dosage units.

Standard: Generally, the weight variation should not exceed ±5% of the average weight of tablets.

Hardness:

Tablet hardness is a measure of tablet strength and integrity.

Standard: The hardness should typically be in the range of 4-10 kg/cm².

Disintegration Time:

Disintegration time measures the time it takes for a tablet to break down into smaller particles in a specific medium.

Standard: Disintegration time should generally be within 15-30 minutes.

Dissolution Testing:

Dissolution testing evaluates the rate at which the drug is released from the dosage form.

Standard: The dissolution profile should be designed to release Metformin in a controlled manner. Specific requirements can vary based on the desired pulsatile release pattern.

Particle Size:

Particle size affects the dissolution rate and bioavailability of the drug.

Standard: Particle size distribution should be controlled to ensure a consistent and desired release profile.

Friability:

Friability measures the tendency of tablets to chip, crack, or break.

Standard: The friability should typically be less than 1% to ensure tablet integrity during handling and packaging.

Content Uniformity:

Content uniformity ensures consistent drug content in each tablet.

Standard: The content of Metformin in individual tablets should generally be within ±10% of the label claim.

Pulsatile Release Evaluation:

This is a specific test to assess the pulsatile drug release pattern from the dosage form.

Standard: The system should demonstrate a significant release after a lag time, simulating the desired pulsatile effect.

EXCIPIENT PROFILE:-

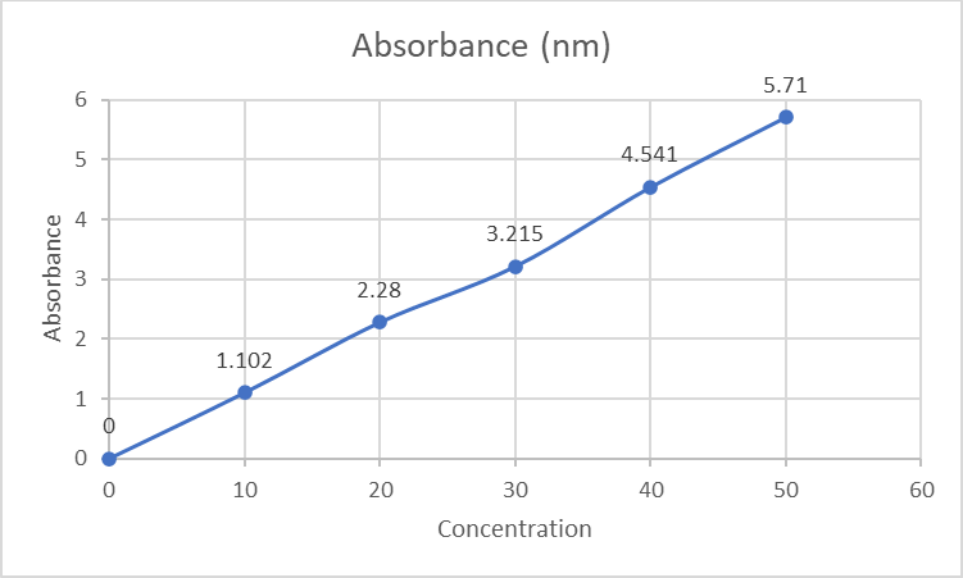
Microcrystalline Cellulose (MCC):
Function: MCC is a commonly used filler and binder in tablet formulations.
Benefits: MCC enhances tablet hardness, provides mechanical strength, and improves disintegration.
Crosscarmellose Sodium:
Function: Crosscarmellose Sodium is a superdisintegrant widely used in tablet formulations.
Benefits: Crosscarmellose Sodium promotes rapid tablet disintegration and enhances drug dissolution.
Crospovidone:
Function: Crospovidone, also known as Polyplasdone, is a commonly used tablet disintegrant.
Benefits: Crospovidone promotes tablet disintegration by absorbing water and swelling rapidly.
Sodium Starch Glycolate:
Function: Sodium Starch Glycolate is a widely used tablet disintegrant and binder.
Benefits: Sodium Starch Glycolate facilitates tablet disintegration by absorbing water and swelling, enhancing drug release.
Talc:
Function: Talc is a multifunctional excipient used as a glidant, lubricant, and anticaking agent.
Benefits: Talc improves powder flow, prevents powder adhesion, and enhances tablet compression.
Magnesium Stearate:
Function: Magnesium Stearate is a widely used lubricant and flow enhancer in tablet and capsule formulations.
Benefits: Magnesium Stearate improves powder flow, reduces friction during tablet compression, and aids in ejection from the die.

EVALUATION OF POST COMPRESSION PARAMETERS:-

UV Spectroscopic method for analysis of Metformin:

Table7.3 Calibration dataof drug(metformin)

S.NO	Concentration (ppm)	Absorbance (nm)
1	0	0
2	10	1.102
3	20	2.280
4	30	3.215
5	40	4.541
6	50	5.710



EVALUATION OF POST COMPRESSION PARAMETERS

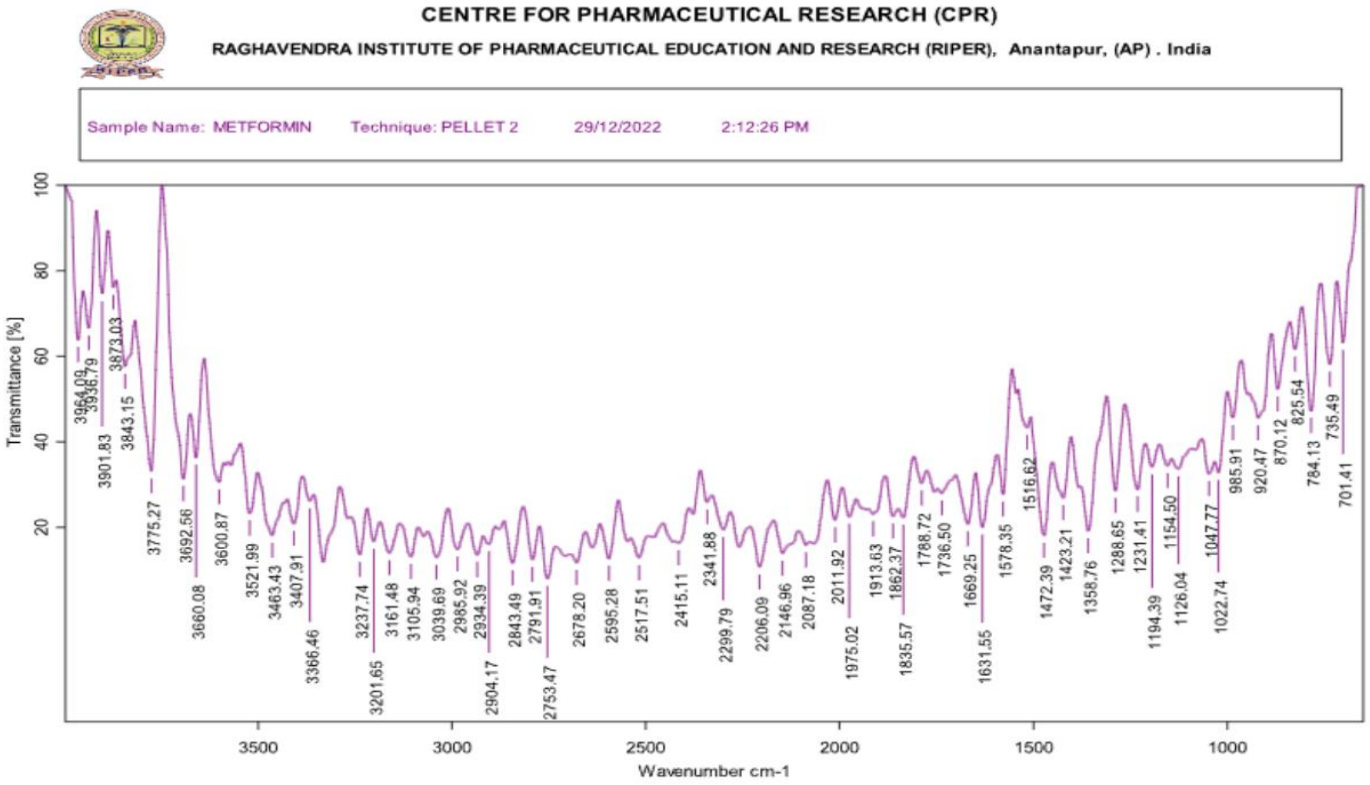
S. No	Physical parameter	F 1	F 2	F 3	F 4	F 5	F 6	F7	F8	F9
1	**Weight (mg)**	152	150	148	149	148	150	149	150	148
2	**Hardness (Kg/cm^2)**	7.3	7.9	7.5	7.2	7.4	7.8	7.4	7.8	7.5
3	**Thickness (mm)**	3.28	3.16	3.82	3.74	3.44	3.25	3.28	3.44	3.25
4	**Friability %**	0.2	0.4	0.2	0.4	0.3	0.5	0.4	0.2	0.5

Drug content uniformity of all formulations

Formulation code	Drug content Avg+- SD (n=3)
F1	99.12+-0.65
F2	98.43+_2.35
F3	99.15+-2.21
F4	97.0.6+-0.93
F5	99.68+-4.28
F6	101.56+-1.612
F7	97.64+-1.612
F8	99.70+-1.86
F9	97.06+-1.32

Metformin hydrochloride tablets contain not less than 90% and not more than 110% of the labeled amount of metformin hydrochloride. Drug content 97.0.6 to 101.56% was found uniform within the batches of different tsblets.

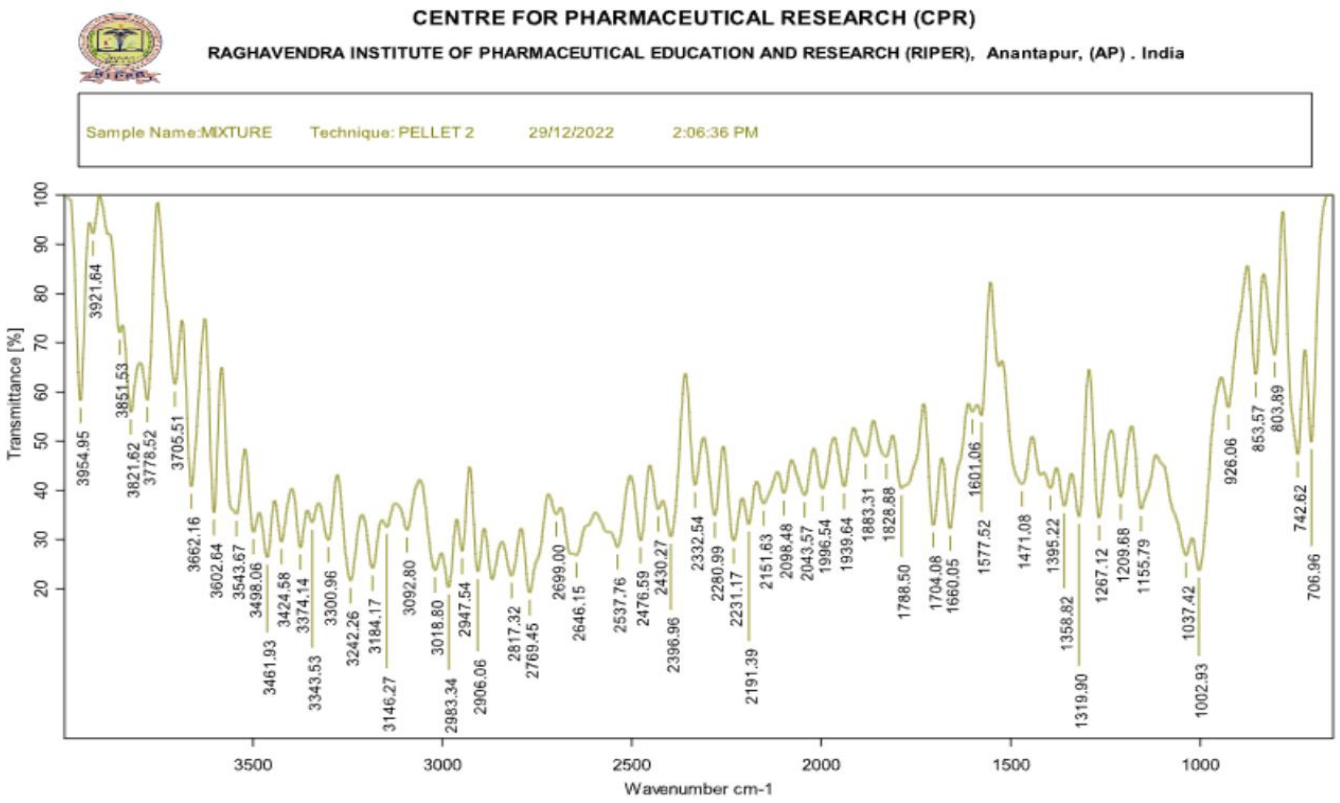
FigFTIRspectraof drug -Metformin



Bond	Vibration Type	Frequency (cm^-1)	Confirmation
C=O	Stretching	1690-1720	Confirms the presence of a carbonyl group
N-H	Stretching	3100-3500	Indicates the presence of an amine group
C-N	Stretching	1220-1340	Confirms the presence of a carbon-nitrogen bond
C-H	Stretching	2800-3000	Indicates the presence of aliphatic or aromatic hydrocarbons
C-N	Bending	660-850	Confirms the presence of a carbon-nitrogen bond
C-C	Stretching	1100-1200	Indicates the presence of carbon-carbon bonds
O-H	Stretching	3200-3600	Indicates the presence of an alcohol or phenol group
N-H	Bending	1450-1650	Confirms the presence of an amine group

Interpretation of metformin .HCL

Excipientsinteraction(FTIR)study:-



Type of Bond	Type of Vibration	Actual Frequency (cm^-1)	Interpretation
(C-O-C) bond	Stretching	1030 - 1150	Presence of cellulose backbone
	Bending	1600 - 1650	
Acid (C=O) bond	Stretching	1680 - 1770	Presence of carboxylic acid group
	Bending	650 - 900	
(C=O) bond	Stretching	1630 - 1690	Presence of amide group
	Bending	700 - 900	
(C=O) bond	Stretching	1650 - 1750	Presence of carboxylic acid group
	Bending	650 - 900	
(Si-O) bond	Stretching	1000 - 1200	Presence of silicate structure
	Bending	500 - 600	
(C-O) bond	Stretching	1300 - 1500	Presence of stearate group
	Bending	600 - 700	

Table:-7.7.Interpretayion of excipoient

Friability values of metformin HCL: -

The Roche Friabilator was used for this test, the device subjects as number of tablets to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25 RPM for 4 minutes by dropping the tablets from the distance of 6 inches with each revolution. Normally a pre weighed ten tablets are placed in the friabilator which is operated for 100 revolutions. The tablets are then dedusted and reweighed.

A maximum loss of weight not greater than 1% present is acceptable for most tablets.

%Friability = (Initial weight –Final weight) ×100 Initial weight

Sl.No	Formulation type	Friability%
1	F1	0.23±0.01
2	F2	0.2 ±0.011
3	F3	0.4 ±0.012
4	F4	0.21 ±0.011
5	F5	0.4 ±0.01
6	F6	0.55 ±0.01
7	F7	0.54±0.012
8	F8	0.2±0.01
9	F9	0.4±0.02

Table: % of Friability

Disintegration values of metformin:-

In vitro Disintegration test: This test is performed to ensure disintegration of core tablets. One tablet is introduced into one tube of disintegration apparatus IP. The assembly suspended in beaker and containing distilled water and apparatus is operated until the tablet get

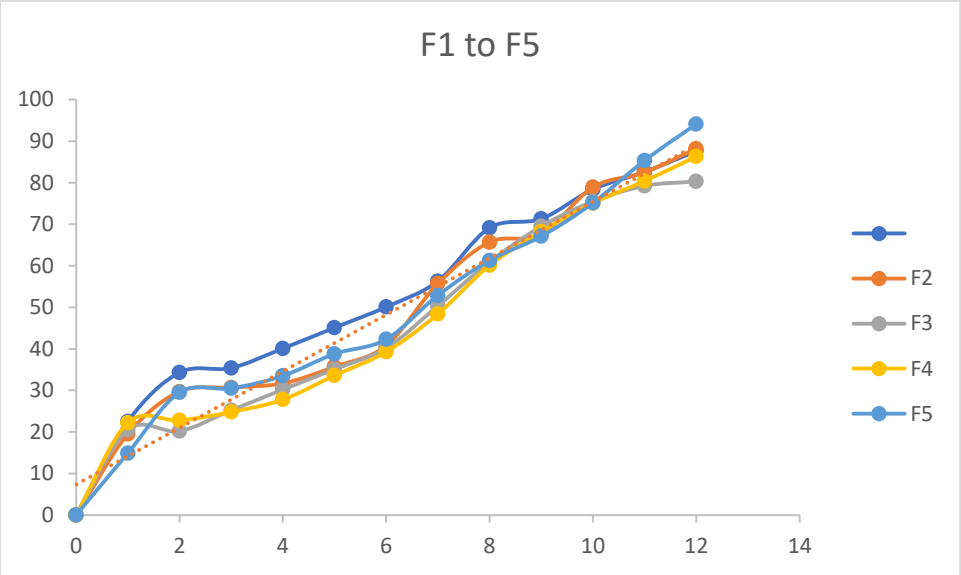
Formulation type	Disinteghration time (min)
F1	14.5
F2	13
F3	14.3
F4	14.1
F5	14.3
F6	13
F7	14
F8	14.5
F9	13.6

disintegrated. The time taken for the complete disintegration of tablet is noted.

Dissolution profile of metformin: -

In-vitro drug release of all formulations:-

Time in hr	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	22.5±2.1	19.5±2.2	20.5±4.1	22.21±3.4	14.9±2.9
2	34.3±2.5	29.7±43	20.2±3.1	22.8±4.0	29.5±3.574
3	35.4±2.53	30.7±4.4	25.2±3.1	24.8±4.0	30.5±35
4	40.1±3.5	31.7±4.8	30.25±2.1	27.8±3.4	33.5±4.4
5	45.1±4.5	35.7±2.1	35.18±3.1	33.6±2.1	38.8±2.8
6	50.1±7.1	40.8±3.1	40.25±34	39.3±8.2	42.3±4.8
7	56.31±6.5	55.7±3.1	50.35±6.5	48.4±8.9	52.9±8.3
8	69.13±8.5	65.75±3.1	60.94±81	60.12±9.1	61.31±21
9	71.31±5.8	67.57±1.3	69.49±4.8	68.29±3.1	67.13±21
10	78.4±4.44	78.9±5.82	75.45±3.12	75.1±3.12	75.13±38
11	82.6±3.41	82.5±2.17	79.25±3.5	80.4±3.92	85.35±48
12	87.6±3.80	88.2±2.86	80.3±3.82	86.31±4.90	94.13±3.5



Time in hr	F6	F7	F8	F9
0	0	0	0	0
1	19.3±2.35	10.9±2.47	13.0±2.81	15.2±2.90
2	26.5±3.7	17.7±2.40	20.9±16	23.6±3.9
3	28.5±37	20.7±2.4	37.2±4.23	24.0±2.1
4	36.5±3.5	30.7±8.5	40.31±4.2	30.05±3.1
5	39.8±4.1	37.1±3.8	45.3±5.3	35.04±8.1
6	43.6±3.5	42.21±8.3	47.3±5.32	37.3±2.03
7	55.62±5.2	51.12±3.8	59.23±35	49.3.5±8.2
8	70.26±2.5	69.31±2.8	70.31±3.5	60.35±8.9
9	71.13±25	72.31±5.2	75.31±14	70.81±90
10	82.5±3.80	78.6±3.48	82.0±2.89	75.31±2.86
11	85.97±4.59	80.6±3.41	91.3±3.66	79.1±3.50
12	87.3±4.90	81.7±2.70	97.0±3.89	80.2±3.80

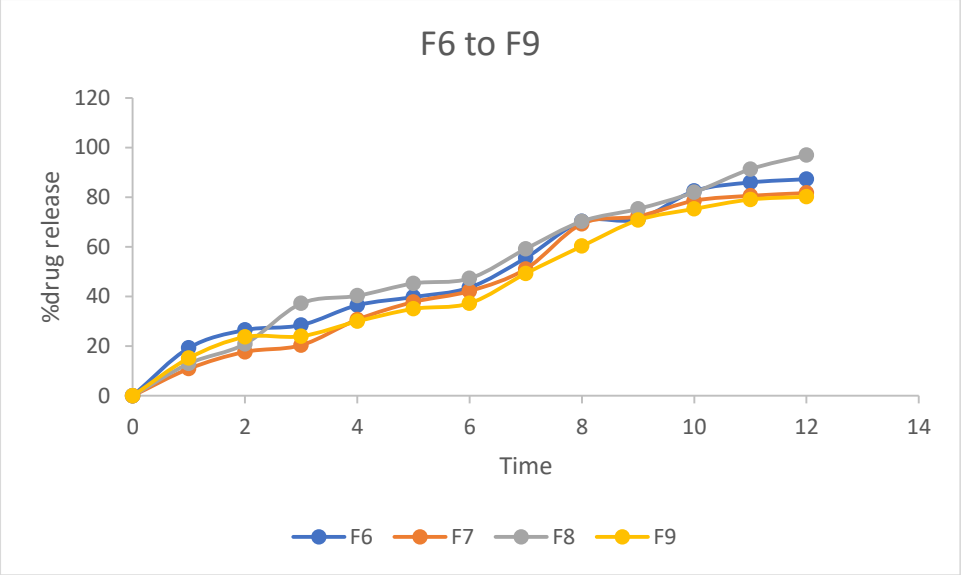


Table5.4MicromeriticpropertiesofPulsatiledrugdeliverysystem ofmetformin:-

Formulation code	Bulkdensity(g/ml)	Tappeddensity (gm/ml)	Carr's index	Hausner ratio	Angleofrepose(^{0})
F1	0.56±0.00049	0.69±0.0099	19.7±0.96	1.23±0.0094	39.8±0.7
F2	0.52±O.00094	0.64±0.0016	17.8±0.33	1.20±0.008	36.6±0.4
F3	0.61±0.012	0.74±0.0016	18.6±1.26	1.25±0.005	38.0±0.6
F4	0.54±0.0058	0.67±0.0061	19.4±0.34	1.24±0.0076	37.3±0.7
F5	0.57±0.0024	0.78±0.0016	18.6±0.66	1.25±0.0034	37.2±0.4
F6	0.63±0.0033	0.79±0.0016	19.2±0.87	1.23±0.0056	38.1±0.9
F7	0.55±0.00034	0.74±0.0015	19.2±0.67	1.23±0.0045	37.2±0.6
F8	0.57±0.00034	0.67±0.0045	18.5±0.78	1.25±0.0056	38.1±0.5
F9	o.49±0.00098	0.74±0.0046	19.9±0.45	1.24±0.0054	36.1±0.8

CONCLUSION

The formulation and evaluation of a pulsatile drug delivery system for metformin using direct compression and a combination of excipients were conducted. Among the different formulations, F5 demonstrated promising characteristics with the desired pulsatile drug release pattern, rapid disintegration, satisfactory hardness, and low friability.

These findings highlight the potential of the pulsatile drug delivery system for metformin, offering opportunities for optimizing therapeutic outcomes and patient compliance in the treatment of type 2 diabetes.

Further studies and development are warranted to refine the formulation and advance its practical application.

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