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TO FORMULATION AND EVALUATION OF SUSTAINED RELEASE TABLET CHLORPROMAZINE

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ABSTRACT:

The goal of this work was to create chlorpromazine HCl sustained release matrix tablets employing a variety of polymers, including HPMC, MCC, and PVP. Following a number of formulations, the powder combinations' qualities were examined and found to have good compressibility and flow characteristics. Tablets with higher concentrations of HPMC and MCC demonstrated longer drug release for up to 24 hours, according to the in vitro release assays. Modulating the drug release rates was also greatly aided by the tablets' swelling behavior; formulations with larger polymer concentrations created a sustained release profile, whereas those without crosslinking agents released drugs more quickly.

keywords: chlorpromazine, sustained release, HPMC, MCC, drug release.

1. INTRODUCTION : [1-7]

For many decades, the treatment of acute or chronic disease has been primarily achieved by administering drugs to patients using various pharmaceutical dosage forms, including tablets, capsules, pills, suppositories, creams, ointments, liquids, sprays and injectables, as a drugs. Carriers: This type of drug delivery system is known to provide quick release of medication or immediate release of a product. Immediate-release products result in rapid drug absorption and the onset of pharmacodynamic effects. Once the drug has been fully absorbed from the dosage form, the plasma concentrations of the drug decrease, which aligns with the expected pharmacokinetic profile of the drug. Eventually, the levels of the drug in the blood decrease below the minimum effective concentration (mec), resulting in a decrease in its therapeutic effects. Before the desired therapeutic effect is achieved, another dose is usually administered if a prolonged effect is required. An alternative to giving another dose is to use a dosage form that releases the drug slowly, keeping the drug levels in the blood higher than what's usually observed with immediate-release forms.

1.1. Modified Release Dosage Form and Drug Delivery[3, 8]:

For many years, there have been medications that alter the rate of drug absorption in order to decrease the frequency of delivery. Intramuscular or subcutaneous injections of insoluble drug complex suspensions, such as procaine penicillin, zinc protamine insulin, or zinc insulin suspension, or injections of the drug in oil, were frequently the first modified release products. Fluphenazine decanoate, for instance. A novel modified release

dosage form is the result of technological advancements. Modified release products offer either continuous or delayed release of the medication, in contrast to traditional versions (instant release).

1.2. Sustained release:

A "sustained release dosage form is one that permits a reduction in dosing frequency from that required for a conventional dosage form, such as a solution or form. immediate release dosage," according to the US Food and Drug Administration (FDA). In contrast to comparable traditional formulations that may require three or four daily doses to produce the same therapeutic effect, extended-release tablets and capsules are often taken just once or twice daily.

1.1.1 Pharmacokinetic Simulation Of Sustained Release Products :

Many sustained-release products' plasma drug concentration patterns fit a one-compartment oral model that is predicated on first-order absorption and elimination. A prolonged release product's absorption rate is usually consistently lower than that of an immediate release product because of its delayed absorption. The maximum drug concentration (Cmax) is often lowered and the duration to maximum concentration (tmax) is typically extended.

1.1.3. Terminology and extended release concept[3,9-15]:

Manufacturers have used a variety of terminology (and acronyms) over the years to describe the types and attributes of products, including timed release (TR), sustained release (SR), sustained action (SA), long action (PA), controlled release (CD), extended release (ER), and ad long-acting (LA). These phrases are used to describe drug delivery systems that are intended to initiate a long-lasting therapeutic impact by continually releasing medications for a long time after a single dose. This period might range from a few days to many months in the case of the injectable dose type.

Sustained Release

Even if the active ingredient discharge in sustained release (SR) dosage forms is smaller than in traditional formulations, the external surroundings into which it is to be discharged nevertheless have a significant impact.

Controlled Release

Drug release from controlled-release (CR) systems is enough to maintain the therapeutic drug level for a long time, and the discharge profiles are mostly regulated by the unique design and technology of the system. As a result, the active component's discharge should ideally be unaffected by outside influences. In order to provide a steady and reliable release of the active ingredient, the sustained release formulation can be a controlled release formulation.

Prolonged action

In order to extend biological half-life, prolonged or long-acting products are dosage forms that comprise therapeutic compounds that have undergone chemical modification (Lee and Robinson, 1987).

A: Instant release

B: Mechanism

C: Repeated action

D: Extended release

E-Prolonged and regulated release

1.2. CONVENTIONAL DRUG THERAPY[4, 22]

Conventional dose forms often have a variety of disadvantages since the dosing interval is significantly shorter than the drug's halflife.

Depending on the medication's biological half-life, there will be significant peaks and troughs in the drug level unless the dose interval is very short.

2. The patient's adherence to the dosage schedule is critical to the effectiveness of this strategy. Several studies have shown that one of the primary causes of medication therapy's inefficiency or failure is non-compliance.

3. The medicine could not be enough to provide a positive biological response in the early stages of administration, which can be a serious issue in some conditions.

4. Frequent dosage is necessary to maintain relatively constant therapeutic levels for medications with a short biological half-life.

1.3. THEORY OF RELEASE SUPPORTED: [23,17]

The following may be included in the extended-release dosage form: a) Maintenance dose, b) Loading dose

The medicine will be released gradually and kept at the therapeutic level for a long time by the maintenance dosage or available portion. Immediately after delivery, the therapeutic level will be attained while maintaining the loading dosage or the immediately accessible fraction.

B-2: Controlled release formulation:

For a specific amount of time, the controlled release device releases a constant supply of the active component, usually at zero speed, in an amount that is comparable to the amount of the medication that the body eliminates. A system that distributes medications at a set pace, either locally or systemically, for a predefined amount of time is called a perfect regulated drug delivery system.

Preparations of repeated actions

A dosage of the medication is first released right after ingestion; this is usually equivalent to one dose of the conventional drug formulation. A second single dosage is released after a specific amount of time. After some time has passed since the second dosage, a third single dose is delivered in certain formulations.

1.4. CONTROLLED ORAL DISCHARGE SYSTEM [10]

H. Because of its ease of use, ease of administration, increased design flexibility for dosage forms (made possible by the flexibility of gastrointestinal anatomy and physiology), ease of production, and consequently, low cost, the oral route has been the most widely used and effective method for controlled drug administration. For oral usage, controlled-release devices are mostly solid and rely on diffusion, dissolution, or a combination of the two to control the rate of drug release.

A. Continuous release systems

These methods use the conventional pharmaceutical form transit to deliver the medication over a longer length of time via the whole alimentary canal. This category's diverse systems include:

1. Delivery system with solution control
2. A mechanism of diffusion-controlled release

3. Diffusion release and controlled dissolving system
4. Natural process resin: compounds of pharmacological
5. Salts and complexes that dissolve slowly
6. Formulation that is pH dependent
7. Pressure-controlled systems
8. System of hydrodynamic pressure

B. Delayed transit system and continuous release

Together with the release systems that fall under this category, these systems are intended to boost your GIT residency;

1. Modified density structures
2. Systems that adhere to mucosa
3. Systems based on dimensions

C. Delayed release systems

1. These systems are designed to exclusively release medication at a specific location on the GIT. Intestinal delivery systems are the first of two types of delayed release systems.
   2. Systems for colon release

   The medications in this system are used by those who are: i. Destroyed in the digestive tract or stomach. ii. Known to upset the stomach
   iii. Taken up from a specific intestinal location, or iv. Meant to have an area impact on a specific gastrointestinal location.

1.4.1. CONTINUOUS RELEASE SYSTEMS: [9,25-27]

Diffusion system:

The sheer fact that the medication release rate is dependent on its diffusion over an inert membrane barrier—typically an insoluble polymer—defines diffusion systems. Diffusion devices may be broadly divided into two categories: matrix devices and tank devices.

(a) Storage devices:

As the name implies, reservoir devices are defined by a polymer membrane enclosing the drug core, or reservoir. The membrane's characteristics dictate how quickly the medication leaves the system. Fick's first law of dissolution governs the release of medication from a reserve device.

1.5. MATRIX SYSTEMS: [21]

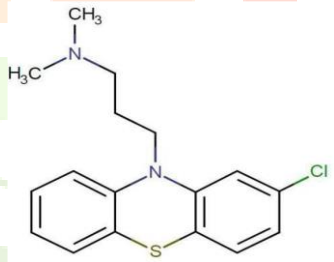
A consistent blend of medication and excipients can serve as a matrix. For instance, a polymer that binds uniformly in a solid dose form. While the matrix is insoluble in the dissolution liquid, the medication, which has a solubility of S gm/cm3, is distributed throughout it.

MATERIALS AND EQUIPMENTS

Materials Used: Microcrystalline cellulose, PVP, HPMC, magnesium stearate, colloidal silicon dioxide, and chlorpromazine HCl

Instruments Used: Tray Dryer, Coating machine, Shaking Water Bath, Tablet Hardness tester, Friability test apparatus, Ultra Violet Visible spectro photometer, FT-IR Spectrophotometer, Tap density Appratus, Granulate Flow Tester, Vernier Caliper, pH Meter, Tablet punching machine.

Drug Profile
Chlorpromazine HCl
Structure:



Molecular Formula : $C_{17}H_{19}ClN_2S.HCl$
Molecular Weight : 318.86 g/mol
IUPAC Name: [3-(2-Chloro-phenothiazin-10-yl)-propyl]-dimethyl-amine
Categories : antipsychotic and antiemetic
Description:

The quintessential antipsychotic medication is phenothiazine. The antipsychotic effects of chlorpromazine, like those of the other medications in this family, are believed to result from the brain's long-term adaptation to dopamine receptor blockage.

Pharmacodynamics:

A psychiatric medication called chlorpromazine is prescribed to treat schizophrenia. It also has antiemetic and sedative properties. Chlorpromazine affects several organ systems and all levels of the central nervous system, mainly the subcortical levels.

Mechanism of action:

Chlorpromazine acts as an antagonist (blocking agent) on different postsysnaptic receptors -on dopaminergic-receptors (subtypes D1, D2, D3 and D4 – different antipsychotic properties on productive and unproductive symptoms), on serotonergicreceptors (5-HT1 and 5-HT2, with anxiolytic, antidepressive and antiaggressive properties as well as an attenuation of extrapypramidal side-effects, but also leading to weight gain, fall in

blood pressure, sedation and ejaculation difficulties), on histaminergic-receptors (H1-receptors, sedation, antiemesis, vertigo, fall in blood pressure and weight gain), alpha1/alpha2-receptors (antisympathomimetic properties, lowering of blood pressure, reflex tachycardia, vertigo, sedation, hypersalivation and incontinence as well as sexual dysfunction, but may also attenuate pseudoparkinsonism - controversial) and finally on muscarinic (cholinergic) M1/M2-receptors (causing anticholinergic symptoms like dry mouth, blurred vision, obstipation, difficulty/inability to urinate, sinus tachycardia, ECG-changes and loss of memory,
However, extrapyramidal side effects may be lessened by the anticholinergic action. A modest presynaptic inhibitor of dopamine reuptake, chlorpromazine can also have minor antidepressant and antiparkinsonian effects. Psychomotor agitation and exacerbation of psychosis, which are infrequently observed in therapeutic use, may potentially be explained by this effect.

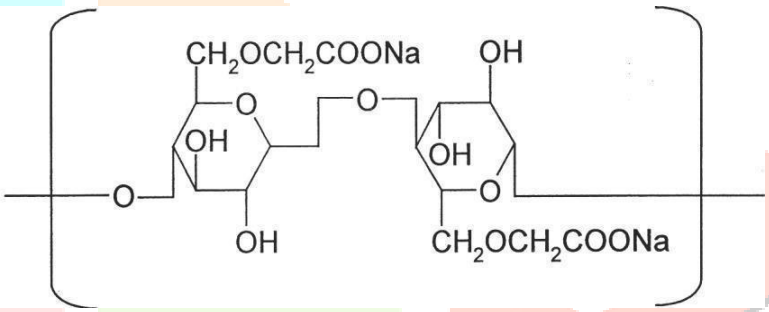
Absorption

quickly absorbed from the gastrointestinal system. The liver's first-pass metabolism causes variations in bioavailability.

POLYMER PROFILE 89-92,61

Hydroxypropyl Methylcellulose:

Other names for it include propylene glycol ether, methylcellulose, methyl hydroxypropylcellulose, and methylcellulose propylene glycol ether. Cellulose, 2-hydroxypropylmethylether, and cellulose hydroxy propylmethylether are its chemical constituents.



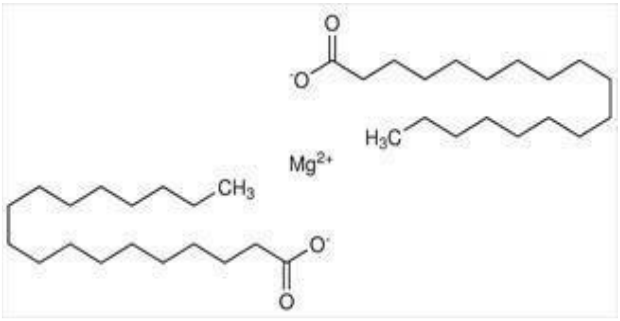
Empirical Formula: $C_8H_{15}O_6 – (C_{10}H_{18}O_6)\ n – C_8H_{15}O_5$
Description: It is an odorless, odorless, white or creamy white fibrous or granular powder.
Molecular weight: 86,000 bulk density 0.25-0.75 g / cm3
Applications:
It serves as a binder (2–5%) and a film former (2–10%). High grades of viscosity They are employed to postpone the release of medications that dissolve in water. In gels and ointments, it also serves as an emulsifier, stabilizer, and suspending agent. adhesive in bandages made of plastic.

2) Microcrystalline Cellulose

Synonyms: Avicel, Emcocel crystalline cellulose
Tablet disintegrant: 5-15% Tablet diluent: 20-90%
Applications:
It is extensively utilized in food and pharmaceutical items. It is employed in both wet granulation and direct compression as a binder or diluent in the production of oral tablets or capsules. It can also be used as a disintegrant or lubricant.

3) MAGNESIUM STEARATE:

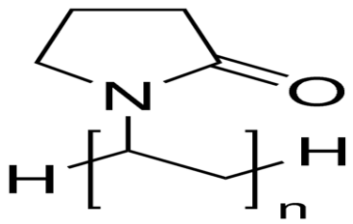
Nonproprietary Names: BP: Magnesium stearate, USP NF: Magnesium stearate
Synonyms: Magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt.
Empirical Formula and Molecular Weight: C36H70MgO4, 591.34 g/mol
Structural Formula



Chemical Name: Octadecanoic acid magnesium salt
IUPAC Name: Magnesium octadecanoate Functional Category: Tablet and capsule lubricant. Physical Properties
Crystalline forms: high-purity magnesium stearate has been isolated as a trihydrate, a dihydrate, and an anhydrate.
Density (bulk): 0.159 g/cm3 Density (tapped): 0.286 g/cm3 Density (true): 1.092 g/cm3
Flowability : Poorly flowing, cohesive powder.

4) Colloidal Silicon Dioxide
Synonyms: aerosil, Cab-O-sil, colloidal silica, fumed silica.
Description:
With a particle size of roughly 15 nm, it is submicroscopic pyrogenic silica. It is an amorphous, light, loose, bluish-white, tasteless, and odorless powder that does not break.
Functional categories:
Adsorbent, anti-caking agent, anti-caking agent, suspending agent, tablet disintegrant, viscosity enhancing agent.
Applications:
Food, cosmetic, and pharmaceutical products all make extensive use of it. It functions as a cursor. Additionally, it serves as a thixotropic suspending and thickening agent in gels and semisolid preparations, as well as stabilizing emulsions. It can also be used to break apart tablets. It is used in aerosols, with the exception of inhalation ones, to decrease spray nozzle clogging, promote particle suspension, and remove hard sedimentation.

5) P0LY VINYL PYRROLIDONE
Synonym: Plasdone k-30, luviskol k-30, plasdone, povidone, polyvinylpyrrolidone p, polyvinylpyrrolidone k-30, polyvinylpyrrolidone; poly (1-(2-oxo-1-pyrrolidinyl)ethylene); povidone k-30; poly(n-vinylbutyrolactam); poly(1-vinylpyrrolidinone)
Chemical name: Poly (1-vinyl-2-pyrrolidinone)
Chemical formula: (C6H9NO)n
Structure:



Functional category: Suspending agent, tablet binder.
Molar mass: 2.500-2.5000.000g.mol-1
Density: 1.2 g/cm3 Melting point: 150-1800C Boiling point: 1930C

EXPERIMENTAL WORK
Preformulation Studies
The first stage in the logical creation of dosage forms for a pharmacological ingredient is the preformulation test. It is the study of a drug's physical and chemical characteristics both by itself and in combination with

excipients. Preformulation testing's main objective is to produce data that will help formulators create stable, bioavailable, and mass-producible dosage forms.

Analytical method used in the determination of Chlorpromazine HCl.

The UV spectrophotometric method was developed for drug analysis using the Shimadzu 1800 spectrophotometer.

Preparation of the phosphate buffer solution at pH 6.8:

A) Preparation of 0.2 M potassium dihydrogen phosphate

To get 0.2 M of potassium dihydrogen phosphate, 27.22 g of the compound were weighed out and diluted with 1000 ml of distilled water.

B) Making the phosphate buffer solution at pH 6.8: In a 200 ml volumetric flask, 50 ml of the 0.2 M potassium dihydrogen phosphate solution was taken out of the stock solution. Next, 22.4 ml of sodium hydroxide solution was added from the stock solution or sodium hydroxide solution, 2M, and the volume was adjusted using distilled water.

To determine λmax, 1% w/v chlorpromazine HCl was produced in water, and the double beam UV spectrophotometer (Shimandzu-1800) was used to scan the maximum absorbance in the 200–400 nm range using 0.1 N as Nothing. It was discovered that the drug's λmax was 250 nm.

Chlorpromazine hydrochloride standard curve

The initial stock solution was made by carefully weighing out 100 mg of chlorpromazine HCl and dissolving it in 100 ml of water. To create the stock solution II, 10 milliliters of the aforementioned solution were collected and diluted to 100 milliliters using the same solvent. 5 µg, 10 µg, 15 µg, 20 µg, 25 µg, and 30 µg of drug per milliliter of the final solution were obtained by further diluting the aliquot of stock solution II with water. Next, using water as a blank, the absorbance was measured at 249 nm using a UV spectrophotometer. The absorbance versus concentration graph was plotted.

Compatibility study using FT-IR: [61]

A careful selection of excipients that are added for convenience of administration, support the drug's constant release and bioavailability, and shield it from degradation is essential to the successful formulation of a stable and effective solid dosage form. A Thermo Nicolet FTIR was used for infrared spectroscopy, and the spectrum was captured between 4000 and 400 cm-1. By monitoring any alterations in the drug peaks in the physical spectrum of the drug mixture, IR-spectral investigations were able to identify drug-excipient interaction.

Method: 100 mg of potassium bromide (dried at 40–50 °C) was combined with 3 mg of the weighed medication. To create a clear substance, the mixture was squeezed in a hydraulic press at a pressure of 10 tons tablet. The IR spectrophotometer was used to scan the silt. All pertinent excipients are employed in a similar manner.

EVALUATION OF PREFORMULATION PARAMETERS

Determination of angle of repose [62, 63]

The stimulated frictional forces between the granular particles are shown by the angle of repose. It is the greatest angle that can exist between the grain pile's surface and the horizontal plane:

Tan θ = h / r

Where, θ = the angle of repose, h = height of the dust heap and r = radius of the dust heap

Table no.4 : ANGLE OF REPOSE

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: From a predetermined height, large volumes of powder (mix mix) were poured onto the graph paper via the funnel. The pile's height was measured. A pencil was used to mark the pile's perimeter. Large and small squares inside the circle were used to compute the area of the produced circle. The area of the circle was then used to determine the parameter "r," which was used to calculate the angle of repose.

Determination of apparent density and derived density [63, 64]

A 100 ml graduated cylinder was filled with 20 g of the mixed mixture (W), and the initial volume was noted. At 2-second intervals, the cylinder was dropped 2.5 cm from a height onto a hard surface under its own weight. Until there were no more audible variations, tapping persisted.

Bulk density = W / V_O

Tapped density = W / VF

Bulk density and density under pressure were calculated using the following formulas.
Where, W = weight of the powder mixture,
V_O = initial volume of the powder mixture
V_F = final volume of powder mix 52

Carr's compressibility index (CI):[63, 54]

One crucial metric that may be derived from both bulk and exploited densities is the compressibility index. Theoretically, a material is more fluid if it is less compressible. A material has good flow properties if its values are less than 20%.

$$CI = \frac{(\text{Tapped Density} - \text{Bulk Density}) \times 100}{\text{Tapped Density}}$$

Compressibility Index

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:63

It is determined by the correlation between the apparent density and the threading density and shows the granules' flow characteristics.

Hausner‟s Ratio = Tapped density/Bulk density

Hausner's Ratio

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

Preparation of sustained-release matrix tablets by direct compression method [59]

Chlorpromazine HCl sustained release pills were made using the direct compression technique. Following careful weighing and accurate mixing of the appropriate amounts of medication and excipients, a drilling machine was used to manufacture the matrix tablets by direct compression. There are 100 mg of chlorpromazine HCl in each tablet.

Selected excipients for prototype formulation

Sl.NO	EXCIPIENT	FUNCTION
1	HPMC	Release rate retardant
2	Polyvinylpyrrolidone	Binder
3	Micro Crystalline Cellulose	Diluent
4	Magnesium stearate	Lubricant
5	colloidal Silicon Dioxide	Glidant

Formulation development of Chlorpromazine HCl by direct compression technique

FORMULA CODE(mg)	F1	F2	F3	F4	F5	F6	F7
Chlorpromazine HCl	100	100	100	100	100	100	100
HPMC	30	40	50	60	70	80	100
Colloidal Silicon dioxide	5	10	15	20	25	30	35
PVP	5	6	7	8	9	10	11
Magnesium Stearate	3	3	3	3	3	3	3
Micro crystalline cellulose QS to	**250**	**250**	**250**	**250**	**250**	**250**	**250**

***All quantities are in milligrams (mg) only.**

POST-COMPRESSION EVALUATION PARAMETERS

Evaluation of Chlorpromazine HCl sustains release tablets:

Drug content uniformity, weight change, tablet hardness, friability, thickness, and in vitro drug release with diverse media were among the evaluation characteristics that were applied to the tablets.

Change in weight [63, 65]

To guarantee that a tablet contains the right amount of medication, the weight of the tablet created is regularly measured. To conduct the USP weight variation test, 20 tablets are weighed separately, the average weight is determined, and the individual weights are compared to the average. The tablets satisfied the USP requirement that no tablet deviates from the percentage limits by more than two times and that no tablet is beyond the limits by more than two percent. The table displays the tablet's official USP percent deviation limits.

Weight Variation Limit

Sr. No.	Average weight of tablet (mg)	Maximum % difference allowed
1.	130 or less	10
2.	130-324	7.5
3.	324<	5

Tablet hardness:[63]

The hardness of tablets determines how resistant they are to fracture or shipping under storage, transportation, and handling conditions prior to use. Five randomly selected tablets were subjected to a hardness test. Five determinations' mean hardness was noted.

Friability: [65]

The weight loss of packaged tablets as a result of tiny particles being removed from the tablet surface is sometimes referred to as friability. Friability typically indicates that the elements in the tablet are not cohesive.

Method: After 20 tablets were weighed and their initial weight was noted, they were put in the Roche crusher

and spun for 100 rpm at a speed of 25 rpm. 52 The following formula was used to determine the percentage of friability:

$$\% \text{ Friability} = \frac{\text{Initial weight of the tablets} - \text{Final weight of the tablets}}{\text{Initial weight of the tablets}} \times 100$$

Tablet thickness:[63]
For the tablet to be consistent in size, its thickness is crucial. Vernier calipers were used to measure the thickness. Ten tablets from each formulation batch were measured for thickness in order to make this determination.

Drug content homogeneity: [59]
The average weight was determined by weighing ten tablets from each batch. After crushing each tablet, 80 mg of the medication was ground into a powder and dissolved in 6.8 phosphate buffer, bringing the total volume to 100 ml. Phosphate buffers at pH 6.8 were used to make up the volume after 1 milliliter of the warehousing solution was collected in a 10-milliliter volumetric flask.

Studies on in vitro dissolution: [35,59]
Using the USP-II dissolution device (Paddle) at 50 rpm, in vitro dissolution experiments were conducted. 0.1 N HCl was used as the dissolution media for the first two hours, followed by phosphate buffer at pH 6.8 for the remaining hours, while the temperature was kept at 37 ± 0.50 °C. At time-specific intervals, 5 ml were taken, and the same volume of fresh medium was substituted. The pH 6.8 was used to dilute the gathered samples. filtered and examined using pH 6.8 at 250 nm in a UV spectrophotometer. as a blank. The cumulative drug release rate was calculated.

Details data of dissolution test:

Dissolution test apparatus	USP type II
Speed	50 rpm
Stirrer	Paddle type
Volume of medium	900 ml
Volume withdrawn	5 ml
Medium used	6.8 phosphate buffer
Temperature	37±0.5ºC

RESULTS AND DISCUSSION

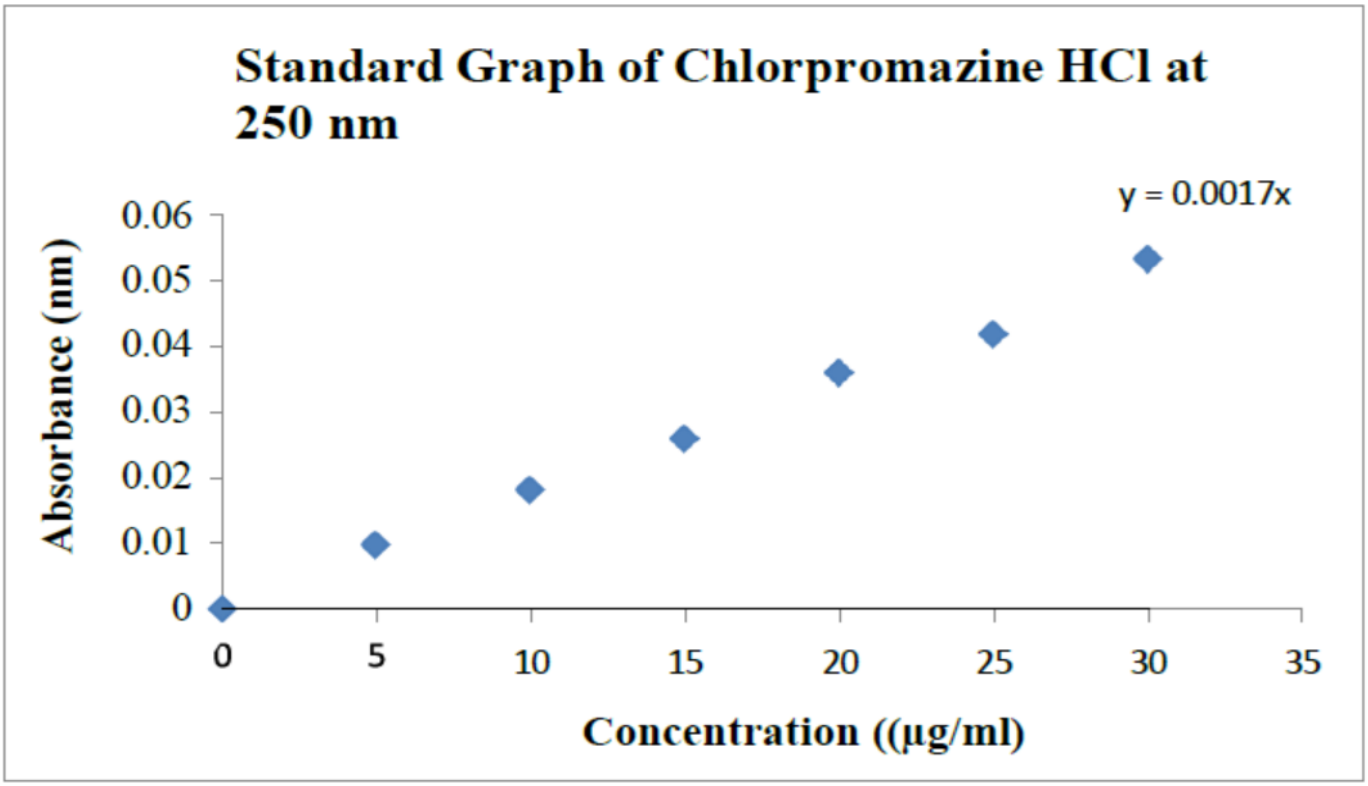
Determination of Chlorpromazine HCl λ max
Chlorpromazine HCl λ max was found to be 250 nm in water.

Chlorpromazine HCl calibration curve

The absorbance of Chlorpromazine HCl was measured on a UV spectrophotometer at 250 nm against water as a blank. The absorbance thus obtained was tabulated (table No. 12) and the graph was obtained by plotting the concentration of the absorbance Vs (figure No.

Spectrophotometric data for the estimation of Chlorpromazine HCl in water

SL. No.	Concentration (µg/ml)	Absorbance at 250 nm				
		Trail-1	Trail-2	Trail-3	Average	S.D.
1	0	0	0	0	0	0
2	5	0.0124	0.0153	0.0153	0.00952	0.00306
3	10	0.0222	0.022	0.0219	0.0189	0.0088
4	15	0.0258	0.0258	0.0252	0.0258	0.00077
5	20	0.0320	0.0331	0.0329	0.0360	0.00350
6	25	0.0369	0.0376	0.0378	0.04174	0.00422
7	30	0.0431	0.0433	0.0434	0.0533	0.00412

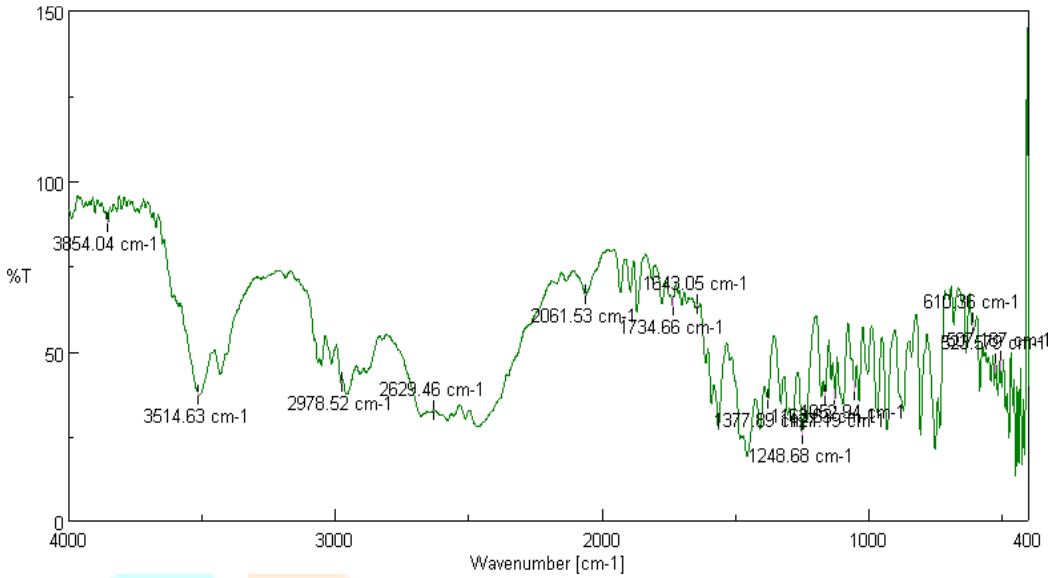


Calibration Curve of Chlorpromazine HCl in water

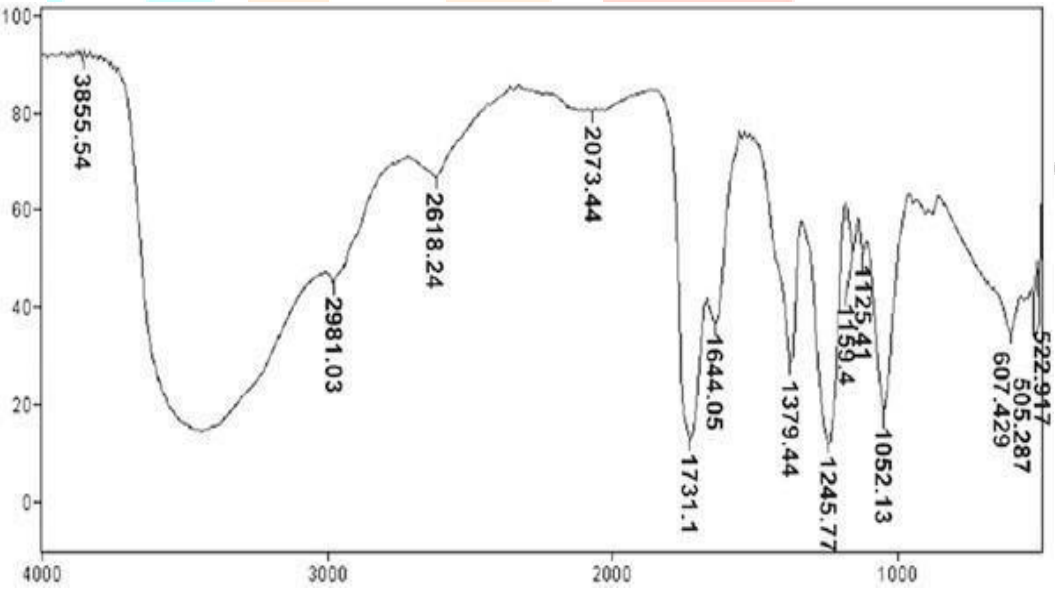
Compatibility studies using FT-IR

Drug-polymer compatibility was demonstrated by the presence of all distinctive peaks of chlorpromazine HCl in the spectra of the drug-polymer mixture.

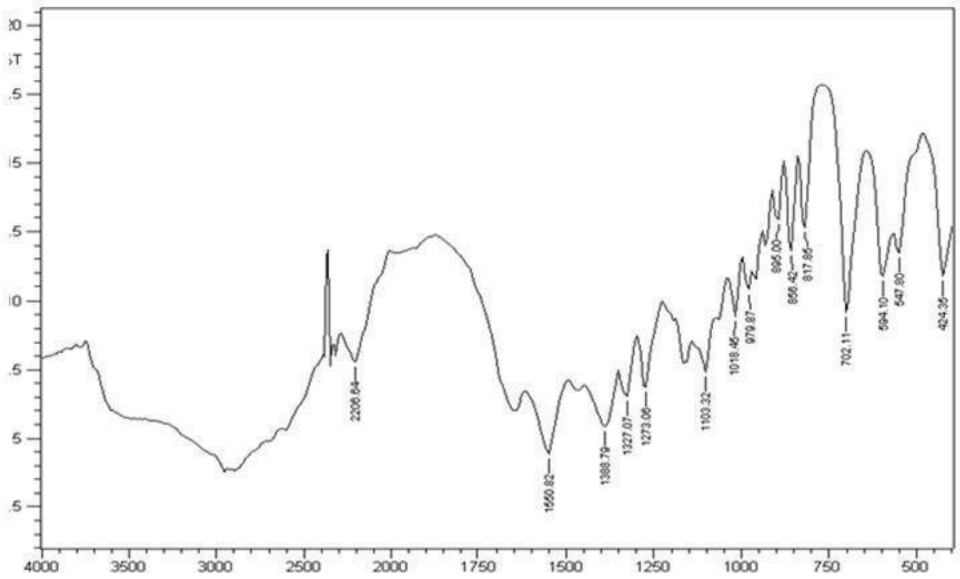
physicochemical combinations of drugs and polymers, suggesting that they were compatible chemically. The spectrum verified that the drug's chemical integrity has not changed significantly.



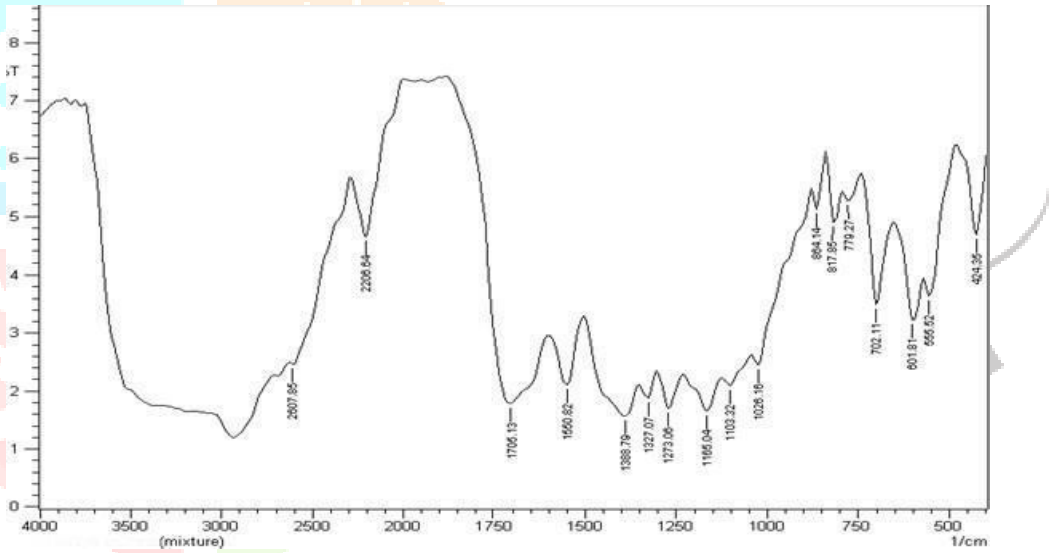
IR Spectrum of Pure Drug Chlorpromazine HCl



IR Spectrum of Microcystalline Cellulose



IR Spectrum of Drug and MCC



IR Spectrum of Drug + other excipients mixtures

FORMULATION DESIGN:

To increase its therapeutic efficacy and reduce side effects by reducing the frequency of dose, the primary goal of this study was to formulate chlorpromazine HCl sustained release matrix tablets utilizing HPMC. In this instance, various polymers, including HPMC, MCC, and PVP, were used in varying amounts to create nine sustained release matrix tablet compositions. Table No. 5 displays each formulation's precise makeup. Prior to and following compression, the powder mixture was evaluated both pre- and post-compression.

Evaluation parameters:

Assessment of the powder mixture's properties for the production of chlorpromazine HCl matrix tablets Mixtures of chlorpromazine HCl and additional excipients were made for each type of formulation, and they The derived density, which ranged from 0.4101 to 0.4880 g/cm3, and the apparent density, which was found to be between 0.355 and 0.3850 g/cm3, show that both parameters were within the range. The Carr compressibility index was computed using the two density values previously published. All powder mixes had excellent to acceptable flow qualities, as shown by the compressibility index and Hausner relationship, which were found to be within the range of 7.27-18.42% and 1.053-1.24, respectively. The angle of repose provides

the best explanation for the flow feature of all powder combinations. All of the powder mixes had good to fair flow characteristics, according to the angle of repose values.

Evaluation parameters of pre-formulation characteristics of powder blend

Formulations Number	Bulk Density (gm/cc)	Tapped Density (gm/cc)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (θ)
F1	0.3712±0.011	0.4101±0.025	7.27±0.659	1.177±0.076	29.73± 0.41
F2	0.3803±0.05	0.4120±0.026	7.58±0.514	1.053± 0.060	25.33 ±0.63
F3	0.3843±0.015	0.4120±0.05	7.43±0.760	1.059±0.088	28.44 ±0.35
F4	0.376±0.020	0.4270±0.037	13.74±0.386	1.073±0.053	27.44 ±0.52
F5	0.355±0.017	0.4600±0.024	15.31±0.794	1.224±0.011	31.34± 0.13
F6	0.3810±0.045	0.4780±0.065	18.42±0.120	1.24±0.020	28.26 ±0.43
F7	0.3850±0.081	0.4384±0.133	10.88±0.301	1.113±0.021	27.27±0.42

Physical evaluation of tablets

Following compression, a number of quality control tests were conducted, revealing the organoleptic qualities of color, smell, and shape. Every formulation (F1 through F7) was concave, rounded, flat, white, and unscented, with a break line on one side.

Organoleptic properties of prepared tablets

Formulation code	Color	Odour	Shape
F1	White color	odourless	Concave, round and flat with break-line on one side
F2	White color	odourless	Concave, round and flat with break-line on one side
F3	White color	odourless	Concave, round and flat with break-line on one side
F4	White color	odourless	Concave, round and flat with break-line on one side
F5	White color	odourless	Concave, round and flat with break-line on one side
F6	White color	odourless	Concave, round and flat with break-line on one side
F7	White color	odourless	Concave, round and flat with break-line on one side

Post-compression parameters results

Formulation	Diameter (mm) ± SD	Thickness (mm) ± SD	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F1	5.82±0.12	3.9±0.91	250.89±0.12	7.3±0.41	0.61±0.17	98.25±0.44
F2	5.80±0.20	4.0±0.21	253.88±0.60	7.8±0.32	0.52±0.22	96.31±0.37
F3	5.85±0.30	4.2±0.12	251.12±0.54	8.0±0.75	0.58±0.11	98.54±0.71
F4	5.84±0.22	3.9±0.73	249.81±0.13	6.5±0.44	0.72±0.16	99.67±0.87
F5	5.90±0.15	4.0±0.41	250.80±0.32	6.8±0.83	0.665±0.19	99.37±0.52
F6	5.94±0.10	3.8±0.93	248.92±0.41	7.1±0.32	0.714±0.12	98.97±0.73
F7	5.97±0.16	4.1±0.17	252.61±0.60	6.0±0.51	0.447±0.01	98.61±0.81

Discussion of physical parameters such as

A. Thickness of tablets
B. hardness
C. friability
D. Weight change
E. Drug content

A. Thickness of tablets

Table No. 16 reports the results of the evaluation of each formulation's thickness using "Calipers" in accordance with the methodological section 4 procedure. All formulations' average thickness was found to be between 3.8 and 4.2 mm, falling within the permitted deviation limit of 5% of the standard value. Additionally, the complete tablet formulation's crown diameter ranged from 8.0 to 7.8 mm.

B. hardness

One of the most important factors in determining how resistant the tablets are to clogging, abrasion, or breaking during handling, storage, and transportation prior to administration is their hardness. Following the steps outlined in section 4 of the methodology, the hardness of each formulation of chlorpromazine HCl controlled release matrix tablet was assessed; the findings are displayed in Table No. 16.

C. friability

The "Roche friabilizer" was used to assess the produced tablets' friability. Table No. 16 displays the results of an evaluation of the percentage friability of each formulation of a controlled release matrix tablet. As a result, F4 showed the highest friability of 0.72%, while F7 showed the lowest friability of 0.447%.

D. Weight variation test:

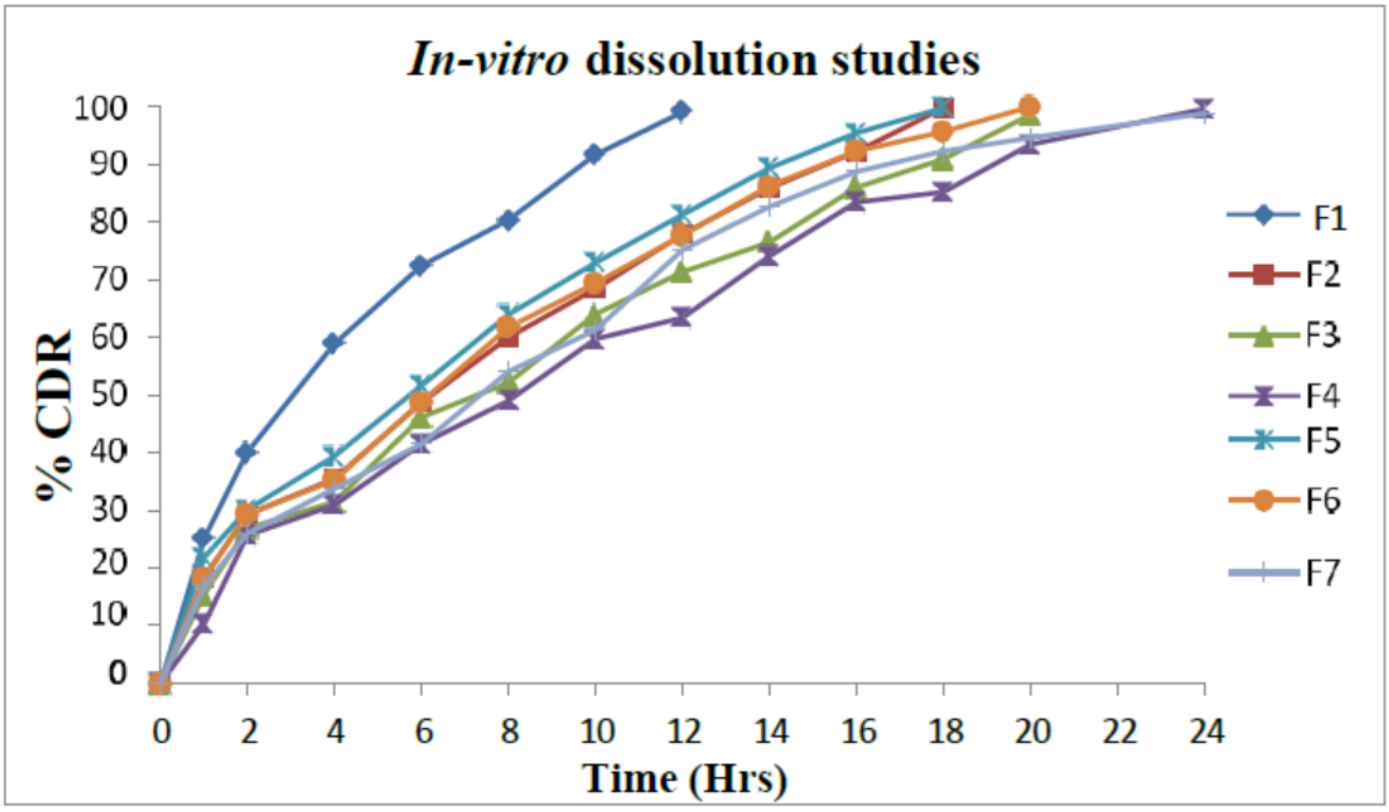
The resulting tablets had a consistent weight since the powder material flowed smoothly, and the mold was filled uniformly with allowable variances in accordance with IP regulations. All of the formulations' weight changes fell between 249.92 and 253.88 mg, and Table No. 16 summarized the findings. Since the percentage of weight change was within the pharmacopoeia's bounds (<5%), all of the prepared tablets passed the weight change test. Every tablet had a consistent weight and a minimal standard deviation.

E. Drug content:

It was discovered that the drug content for formulations F1 through F7 ranged from 98.25% w/w to 99.61% w/w. satisfies official requirements. Table No. 16 displays the findings.

Drug release research in vitro:

To investigate its capacity for continuous release, HPMC was selected as the polymer in this investigation and mixed with PVP and MCC. Table 17 and Figure 10 show the in vitro release statistics for MCC sustained release matrix tablets and chlorpromazine HCl PVP-HPMC. The dissolution media, PVP, MCC, and polymer concentrations had the biggest effects on the in vitro release of chlorpromazine HCl from tablet formulations in the matrix. Another factor influencing the in vitro release of matrix tablets made of chlorpromazine HCl is the tablets' swelling tendency; the more the tablet swells, the less medication is released. and the study was conducted for a full day. In all formulations, the first 6–7 hours had the largest in vitro release of chlorpromazine HCl. After an hour, the PVP-HPMC tablets released between 10.29% and 18.34% of chlorpromazine HCl, the MCC and HPMC tablets released between 16.90% and 21.91%, while the tablets that contained just release retardant polymer released 25.12%. The amount of medicine released was greater at first, but it was delayed by six to seven hours. Since there are no crosslinking agents in Formulation F1, practically all of the medications were released after 12 hours. Lower amounts of HPMC and MCC in formulations F2, F3, F5, and F7 demonstrated almost complete drug release in 16 hours, 20 hours, 16 hours, and 18 hours, respectively. Because the maximum amount of medicine was delivered before the intended time period—24 hours—these formulations were therefore deemed to be poor formulations. This pH 6.8 significantly reduces the ionic interaction between crosslinking agents and negatively charged polymers, resulting in a loose network with an expanding porous surface that permits large portion of the dissolving medium. The release of chlorpromazine HCl is prolonged to 24 hours in formulations F4 and F7, which contain the highest concentrations of HPMC and MCC combined with HPMC, respectively. This could be because the polymeric agent-based crosslinking system's surface has developed a complex film of self-assembled polyelectrolytes. Additionally, the swelling investigation demonstrated that the formulation with a higher crosslinking agent concentration had a longer duration of drug release, up to 24 hours, and a higher swelling capability.



Comparative dissolution profile of the formulations F_1 toF_7

***In-vitro* drug release profile of Chlorpromazine HCl sustain release tablet**

Time (Hrs)	Cumulative Percentage Drug Release						
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F_7**
0	0	0	0	0	0	0	0
1	25.12±0.19	18.34±0.43	15.386±0.33	10.29±0.55	21.91±0.54	18.25±0.32	16.90±0.85
2	40.02±0.12	29.24±0.21	26.905±0.45	25.64±0.62	30.92±0.43	29.25±0.22	25.99±0.42
4	58.82±0.12	35.45±0.33	31.465±0.21	30.94±0.53	39.33±0.54	35.20±0.64	33.71±0.79
6	72.41±0.14	48.71±0.20	46.137±0.13	41.54±0.45	51.64±0.51	48.82±0.73	41.55±0.54
8	80.03±0.28	59.99±0.54	52.186±0.43	48.96±0.33	63.93±0.65	61.73±0.83	54.08±0.64
10	91.61±0.34	68.41±0.55	63.97±0.42	59.68±0.42	72.96±0.72	69.40±0.88	61.27±0.53
12	99.07±0.12	77.09±0.22	71.33±0.54	63.38±0.38	81.23±0.42	77.73±0.95	75.14±0.43
14	--	85.86±0.26	76.50±0.65	74.11±0.43	89.37±0.44	86.24±0.76	82.67±0.42
16	--	92.15±0.33	85.96±0.66	83.39±0.14	95.39±0.62	91.28±0.87	88.75±0.48
18	--	99.71±0.42	90.88±0.59	85.21±0.11	99.77±0.11	95.62±0.73	92.23±0.48
20	--	--	98.54±0.43	93.39±0.14	--	97.99±0.61	94.54±0.48
24	--	--	--	99.54±0.11	--	--	98.78±0.48

SUMMARY AND CONCLUSIONS

SUMMARY

Following an FT-IR compatibility investigation between the medicine and excipients, it was concluded that there was no interaction between the two substances. Numerous prestressing tests, including those measuring angle of repose, bulk density, thread density, Carr index, and Haunser ratio, were performed on all formulations. The findings showed that the powder combinations showed compression and good to fair compression. A variety of post-compression tests have been performed on all formulations, including in vitro dissolution studies, weight changes, hardness, thickness, friability, and drug content. The produced tablets' thickness and hardness were determined to be between 6.0 and 8.0 kg/cm2. Additionally, all other parameters, including 3.5-4.0mm, fell within the official standard requirements. The in vitro dissolution study's findings showed that formulations F4 and F7 had sustained drug release at the end of 24 hours, with 99.54% and 98.78%,respectively.

CONCLUSIONS;

The current study's objective was to determine whether employing varying quantities of crosslinking agents and polymers could facilitate the release of chlorpromazine HCl from the produced tablet. The following conclusions can be made based on the results. 1. Pre-formulation analyses revealed that all formulations' Carr's index, bulk density, Haunser ratio of thread density, and angle of repose were within acceptable ranges. limits.

2. FTIR analyses showed that the medication and other excipients did not interact chemically.

3. After compressing the powder mixes into tablets, postcompression characteristics as weight, thickness, hardness, friability, and drug content change were assessed. Every formulation batch produced results that were

satisfactory.

4. Using a USP type II dissolution device, in vitro drug release was examined over a 24-hour period in intestinal and simulated stomach fluid. The findings demonstrated that formulations with greater concentrations of MCC (F7, 98.78%) and HPMC (F4, 99.54%) sustained drug release for a full day.

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