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FORMULATION DEVELOPMENT AND EVALUATION OF SUSTAINED RELEASE TABLET CHLORPROMAZINE HCL

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ABSTRACT

Chlorpromazine HCl was selected as a candidate for the development of sustained- release tablets. Drugs are often given to patients through the oral route. Patients and doctors alike tend to choose tablets as the best oral formulation currently on the market. Using an extended release dosage form may increase a drug's therapeutic efficacy by maintaining a plasma concentration of the drug that is two- to three-fold higher than when the drug is taken directly. The use of polymers into dosage forms is currently standard practice with the aim of improving drug delivery. The microcrystalline cellulose (MCC) was used as the direct compressible agent, while the magnesium stearate was used not only as a crosslinking agent but also as a lubricant and slip agent. Polyvinylpyrrolidone (PVP) served as a binding agent. The medicine and excipients did not interact negatively, according to the FT-IR study of the two substances. After extensive prestressing research into factors like angle of repose, bulk density, thread density, Carr index, and Haunser ratio, the powder combinations demonstrated compression and good to fair compression. Compression's effects on formulations' weight, hardness, thickness, friability, medicine content, and in vitro dissolution were tested extensively. Preparation results in tablets with a hardness and thickness of 6.0–8.0 kg/cm2. Not only did everything fall inside the accepted range of 3.5–4.0mm, but it also satisfied all other normative requirements. The in vitro dissolution investigation revealed that after 24 hours, the drug release from formulations F4 and F7 was 99.54 and 98.78 percent effective, respectively.

KEYWORD: Chlorpromazine HCl, sustained- release tablets, in-vitro dissolution & HPMC.

INTRODUCTION

Pills, capsules, tablets, suppositories, creams, ointments, liquids, sprays, and injectables are just some of the numerous pharmaceutical dosage forms that have been used to treat acute and chronic diseases for decades. Carriers as its name implies, this kind of drug delivery system is designed to provide instantaneous or fast drug release. Drug absorption and its pharmacodynamic effects are completed rapidly in the case of quick release products.[1,2]

The medication's pharmacokinetic profile was confirmed by the finding that plasma concentrations of the drug decrease once drug absorption from the dose form is complete. Therapeutic effectiveness is lost when drug plasma

concentrations fall below the MEC. If a prolonged therapeutic impact is sought, a second dosage is often administered before this point. Rather of giving the patient another dose, a sustained-release dosage form may be used to keep the drug's concentrations in the bloodstream at a higher level than is found with immediate-release formulations. Multiple updated versions and/or delayed medication releases have occurred in recent years. Due to the benefits of studying the new medicine, the quest for a replacement treatment persisted well beyond the turn of the twentieth century. This has prompted pharmaceutical corporations and academic research facilities to focus on creating new drug delivery systems and modified release dosage forms rather than researching and developing an entirely new medicine.[3,4]

A continuous drug delivery system is developed so that the medication's biopharmaceutical, pharmacokinetic, and pharmacodynamic characteristics may be improved, resulting in minimal adverse effects and rapid disease treatment or control. The dosage, given by the most secure and effective method.[5] By allowing for a regulated and prolonged release and/or by targeting the medication to the defined location, the unique drug delivery system provides a means of enhancing the therapeutic effectiveness of the integrated pharmaceuticals. The purpose of giving a medicine to someone.[6]

A therapeutic dose of the medication is given when the patient is in the ideal posture for achieving and maintaining the desired drug concentration as efficiently as possible. Interest in methods of administering drugs orally over longer periods of time is on the rise in the pharmaceutical sector. Creating a dosage form that can deliver a large dose of the medicine is also of significant relevance.[7] This is especially true for highly water-soluble active components.

Sustained-release delivery systems can be defined as those that require less frequent administration than traditional dose forms like pills or liquids, as stated by the Food and Drug Administration of the United States. A dose that works right away." Since they may be taken once or twice daily instead of three or four times a day as required by the original formulations, extended-release tablets and capsules are becoming more and more popular. "In products with sustained release, the medication is frequently immediately administered to have the intended therapeutic effect and then gradually given in increasing quantities to maintain this effect for a certain amount of time .Patients and caregivers both benefit from the elimination of midnight dosage because to sustained release products' ability to maintain therapeutic plasma concentrations of the active ingredient(s).

By the use of CR technology, pharmaceuticals can be administered in doses that keep the therapeutic drug level stable for an extended period of time. These systems' distinct designs and types of technology largely affect the release profiles of these systems. Therefore, it is preferable if the active component's discharge is unaffected by the environment. Sustained-release formulations, of which controlled-release forms can be one, are made to provide a steady supply of the active ingredient over a prolonged period of time. By contrast, prolonged-release (ER) dosage forms of medications are designed to have a relatively long half-life in the body, typically between 8 and 12 hours after a single dose.

EXPERIMENTAL WORK

Preformulation Studies

Preformulation testing is the first step in developing appropriate dosage forms for a pharmaceutical. In other words, it's the study of how a drug's physical and chemical characteristics change when mixed with excipients. For the formulator to develop a stable, bioavailable, and marketable dosage form, they need data obtained from preformulation testing.

EVALUATION OF PREFORMULATION PARAMETERS

Determination of angle of repose[8,9]

Excited frictional forces between the granular particles may be seen in their angle of repose. Preformulation testing is the first step in the systematic process of developing a drug's dosage forms.

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

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

Table No 1: 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: The funnel was used to dump large quantities of powder (mix mix) from a fixed height onto the grid paper. Using a measuring stick, they were able to calculate the height of the pile. The size of the mound was calculated by drawing a circle around it. Before determining the angle of repose, we calculated the area of the circle by adding the areas of the large and small squares included within the circle. This gave us the parameter "r," which we then used to get the angle of repose.

Determination of apparent density and derived density[9,10]

A 100 ml graduated cylinder was filled with 20 grammes (W) of the combined substance. A cylinder was dropped with its whole weight on it from a height of 2.5 cm onto a hard surface at regular intervals of 2 seconds. Up until there were no audible changes, tapping persisted. The following formulae were used to get the bulk density and the density under pressure.

Carr's compressibility index (CI):[9,10]

Using the density and the utilisation density, one can determine the compressibility index, which is a helpful parameter. In principle, a substance is more fluid and less compressible. Materials with percentages lower than 20% have favorable flow properties.

Hausner's Ratio:[9] Measured by the correlation between the threading density and the apparent density, it provides insight into the granules' flow behavior.

Direct compression method for making long-acting matrix tablets[11]

Chlorpromazine HCl sustained-release tablets were made using the direct compression process. A drilling machine was used to make the matrix tablets by direct compression after the correct dosage of the medication and excipients had been measured and combined. Chlorpromazine HCl 100 mg is the active ingredient in each tablet.

Table no 2: 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

Table no 3: Formulation development of Chlorpromazine HCl.

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**

POST-COMPRESSION EVALUATION PARAMETERS

Evaluation of Chlorpromazine HCl sustains release tablets

The tablets were tested for a number of qualities before being released onto the market, such as how well they released their active ingredients in vitro and how stable their weight and thickness remained over time.

Weight shift[9,12]

To make sure a tablet contains the right quantity of medication, the weight of the created tablet is frequently measured. The USP weight variation test requires the weighing of 20 tablets individually, the calculation of an average weight, and a comparison of the individual tablet weights to the calculated average. No more than two tablets deviated from the specified percentages, and no two tablets deviated by more than twice the specified percentages, demonstrating that the tablets met the USP criterion. The tablet shows the authorized USP percent deviation limits.

Table no 4: 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[6,3]

The hardness of tablets determines how well they will hold up throughout storage, transit, and handling before to use. Each batch of tablets was subjected to the Monsanto hardness tester to determine their relative hardness. Kg/cm2 was used as the unit of measurement for hardness. A random sample of 5 pills was selected and their hardness was evaluated. Following five separate measurements, an average hardness was recorded.

Friability[12]

A tablet's friability is measured by its ability to shed weight after being packed as a result of the removal of dust and other small particles from its surface. Friability often indicates the disorderly nature of the constituents in tablets.

Method: 20 pills were weighed and their starting weight recorded before being put in the Roche crusher and spun at 25 rpm for 100 rpm. After taking them out of the shredder, the pills were dusted for any remaining fine particles, weighed

again, and their new total was recorded. 52 A formula was used to determine the degree of friability:

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

Tablet thickness[9]

In order to ensure consistency in tablet size, the thickness of the tablet is crucial. Vernier calipers were used to determine the thickness. The thickness of ten tablets from each batch of the formulation were measured.

Uniformity of drug content[11]

The average weight of 10 pills from each batch was determined. The pills were ground into a powder and then dissolved in 100 cc of phosphate buffer with a pH of 6.8. The 1 ml of solution extracted from the storage solution and placed in a 10 ml volumetric flask was then buffered with the 10 ml of pH 6.8 phosphate solution. A spectrophotometric reading of 250 nm was taken of the filtered solution against a standard of phosphate buffer at pH 6.8. A tablet's worth of medication was figured out.

RESULTS AND DISCUSSION

Evaluation parameters

Formulation of matrix tablets containing Chlorpromazine HCl: powder mixture characteristics evaluation Chlorpromazine HCl was combined with additional excipients for each formulation type and then evaluated for a number of different properties, including bulk density, plugging density, compressibility index of Carr, Hausner relationship, and rest corner. The computed density ranged between 0.4101-0.4880 g/cm3, while the apparent density was found to be between 0.355 and 0.3850 g/cm3. The Carr compressibility index was determined using the previously reported density differences". All powder mixes were found to have excellent to acceptable flow qualities, with the compressibility index ranging from 7.27 to 18.42% and the Hausner relationship from 1.053 to 1.24. The angle of repose is the most universally applicable description of the flow attribute of powder mixes. Repose angles were measured and found to be between 25.33 to 31.43 degrees. All of the powder combinations tested exhibited excellent to acceptable flow characteristics, as seen by the angle of repose.

Table no. 5: 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 tablet

The organoleptic qualities, including color, fragrance, and shape, were confirmed by a battery of quality control tests performed after compression. All seven iterations (F1 through F7) were identical in form, with a uniformly white color, a lack of discernible odor, and a concave, rounded, flat form with a distinct break line along side.

Table no. 6: 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

Table no. 7: 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

Table 8: *In-vitro* drug release profile of Chlorpromazine HCl sustain release tablet.

Time (Hrs)	Cumulative Percentage Drug Release						
	F1	F2	F3	F4	F5	F6	F7
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

CONCLUSION

The purpose of this research was to examine the efficacy of utilizing varying doses of crosslinking agents and polymers to aid in the release of Chlorpromazine HCl from the prepared tablet. The data collected may be used to draw the following conclusions. Pre-formulation studies showed that the formula's key properties, including angle of repose, bulk density, Haunser ratio of thread concentration, and Carr's index, were all well within the expected ranges. After being formed from the powder mixtures, the tablets were crushed and analysed for changes in their weight, thickness, hardness, friability, and drug content. There were absolutely no batches of the formulation that were defective. The in vitro drug release was examined over a 24-hour period in both intestinal fluid models and stomach fluid models using a USP class II dissolving device. Formulations with a greater concentration of HPMC (F4, 99.54%) and MCC (F7, 98.78%) were shown to sustain drug release for 24 hours.

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