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. The oral route is the most used route for the administration of drugs. Tablets are the most popular oral formulations available on the market and are preferred by patients and physicians. Extended release dosage forms have been shown to improve therapeutic efficacy by maintaining a constant 2-3 fold plasma concentration of the drug. The use of polymers to support drug delivery has become an important tool in the formulation of dosage forms. Sustainable release can be achieved using HPMC together with crosslinking agents and other excipients used were PVP as binding agent, MCC as direct compressible agent and magnesium stearate as slip and lubricant respectively. The drug and excipients were subjected to a compatibility study using FT-IR, which suggested that there was no interaction between the drug and the excipients. All formulations were subjected to various prestressing studies, such as angle of repose, bulk density, thread density, Carr index, Haunser ratio, and the results revealed that the powder mixtures exhibited compression and good to fair compression. . All formulations have undergone various post-compression studies, including weight changes, hardness, thickness, friability, drug content, and in vitro dissolution studies. The hardness and thickness of the prepared tablets were found in the range of 6.0 to 8.0 kg / cm2. And 3.5- 4.0mm and all other parameters were within the official standard specifications. The results of the in vitro dissolution study indicated that the drug release of formulation F4 and F7 showed 99.54% and 98.78% respectively at the end of 24 hours in a sustained manner.

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

INTRODUCTION

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 injectable, as a drug Carriers. This sort of drug delivery system is understood to supply rapid release of drug or immediate release product. Such immediate release products end in relatively rapid drug absorption and associated pharmacodynamic effects.[1,2] However, once drug absorption from the dosage form is complete, the plasma

concentrations of the drug decrease supported the pharmacokinetic profile of the drug. Eventually, the plasma concentrations of the drug drop below the minimum effective plasma concentration (MEC), leading to a loss of therapeutic activity. Before now is reached, another dose is typically given if a protracted therapeutic effect is desired. An alternate to administering another dose is to use a dosage form that gives sustained release of the drug and thereby maintains plasma drug concentrations beyond what's typically seen with immediate-release dosage forms. In recent years, several modified versions and / or the time of release of the drug. After the 20th century, the look for a replacement drug remained thanks to the value of researching the new drug. Therefore, pharmaceutical industries and academic laboratories have focused on creating a replacement drug delivery system / or modified release dosage forms instead of research and development of a replacement drug.[3,4]

The rationale for a protracted drug delivery system is to optimize the biopharmaceutical, pharmacokinetic and pharmacodynamic properties of a drug such its usefulness is maximized by reducing side effects and treating or controlling the disease as quickly as possible using the foremost little ones. Amount of drug, administered by the foremost appropriate route.[5] The novel drug delivery system offers a way of accelerating the therapeutic efficacy of incorporated drugs by providing a controlled and sustained release and / or by targeting the drug to the specified site. The goal of any drug administration[6]:

The system consists of administering a therapeutic amount of drug within the correct position of the body to rapidly reach and thus maintain the specified drug concentration. There is a growing interest in the pharmaceutical industry for extended-release oral drug delivery systems. There is also a great deal of interest in designing a dosage formulation that allows for a high drug load, particularly for active ingredients with high water solubility.[7]

The United States Food and Drug Administration (FDA) defines a "sustained release dosage form as one that allows for a reduction in dosing frequency from that required for a conventional dosage form, such as a solution or form. Immediate release dosage." Extended-release tablets and capsules are commonly taken only once or twice a day, compared to equivalent conventional forms which may need to be taken three or four times a day to achieve the same therapeutic effect. Typically, sustained release products provide immediate drug release that rapidly produces the desired therapeutic effect, followed by the gradual release of additional amounts of drug to maintain this effect for a predetermined period. Sustained plasma drug levels often provided by sustained release products eliminates the need for overnight dosing, which benefits not only patients but also the care provided.

Controlled-release (CR) systems provide drug release in an amount sufficient to take care of the therapeutic drug level for an extended period of your time, with the discharge profiles predominantly controlled by the system's special construction and style technology. Therefore, the discharge of the active component is ideally independent of external factors. The sustained release formulation may be a controlled release formulation designed to supply a consistent and constant release of the active ingredient. Prolonged-release (ER) dosage forms are people who, because of the special technology of preparation, provide, immediately after the administration of one dose, the therapeutic levels of the drug are maintained for 8-12 hours.

EXPERIMENTAL WORK

Preformulation Studies

The preformulation test is the first step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of the physical and chemical properties of a drug alone and when combined with excipients. The overall goal of preformulation testing is to generate information useful to the formulator in the development of stable and bioavailable dosage forms that can be mass produced.

EVALUATION OF PREFORMULATION PARAMETERS

Determination of angle of repose[8,9]

The angle of repose is an indication of the excited frictional forces between the granular particles. It is the maximum possible angle between the surface of the grain pile and the horizontal plane:

$$Tan\ \theta = h\ /\ r$$

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: Heavy amounts of powder (mix mix) were poured through the funnel from a fixed height onto the graph paper. The height of the pile was measured. The circumference of the pile was marked with a pencil. The area of the formed circle was calculated on the basis of the large and small squares present within the circle and then the angle of repose was calculated on the parameter "r" which was identified by the area of the circle.

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

20 g of the mixed mixture (W) were placed in a 100 ml graduated cylinder and the initial volume was observed. The cylinder was dropped under its own weight onto a hard surface from a height of 2.5 cm at 2 second intervals. Tapping continued until no further volume changes were observed. Bulk density and density under pressure were calculated using the following formulas.

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

The compressibility index is an important measure that can be obtained from bulk and exploited densities. In theory, the less compressible a material is, the more fluid it is. A material with values below 20% has good flow property.

Hausner's Ratio:[9] It indicates the flow properties of the granules and is measured by the relationship between the threading density and the apparent density.

Preparation of sustained-release matrix tablets by direct compression method[11]

Sustained release tablets of Chlorpromazine HCl were prepared by direct compression method. The corresponding amount of drug and excipients was carefully weighed and mixed properly and the matrix tablets were prepared by direct compression using a drilling machine. Each tablet contains 100 mg of Chlorpromazine HCl.

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 subjected to various evaluation parameters, including drug content uniformity, weight change, tablet hardness, friability, and thickness, and in vitro drug release with different media.

Weight shift[9,12]

The weight of the tablet produced has been routinely determined to ensure that a tablet contains the correct amount of drug. The USP weight variation test is performed by weighing 20 tablets individually, calculating the average weight, and comparing the individual weights with the average. The tablets met the USP specification that no more than 2 tablets are outside the percentage limits and no tablet differs by more than twice the percentage limit. The tablet's official USP percent deviation limits are presented.

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[63]

The resistance of tablets to shipping or breakage under the conditions of storage transport and handling before use depends on their hardness. The hardness of each batch of tablets was tested using the Monsanto hardness tester. Hardness was measured in terms of kg / cm2. 5 tablets were chosen at random and tested for hardness. The mean hardness of 5 determinations was recorded.

Friability[12]

Friability generally refers to the loss of weight of packaged tablets due to the removal of fine particles from the tablet surface. Friability generally reflects the poor cohesion of the tablet ingredients.

Method: 20 tablets were weighed and the initial weight of these tablets was recorded and placed in the Roche crusher and rotated at the speed of 25 rpm for 100 rpm. The tablets were then removed from the shredder, the fine particles were dusted off and weighed again and the weight was recorded. The percent friability was calculated using the

formula:

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

Tablet thickness[9]

The thickness of the tablet is important for uniformity in the size of the tablet. The thickness was measured using vernier calipers. It was determined by checking the thickness of ten tablets from each batch of formulation.

Uniformity of drug content[11]

10 tablets from each batch were weighed and the average weight was calculated. All tablets were crushed and a powder equivalent to 80 mg of the drug was dissolved in 6.8 phosphate buffer and the volume made up to 100 ml with pH 6.8 phosphate buffer. From the warehouse solution, 1 ml of solution was collected in a 10 ml volumetric flask and the volume was made up with phosphate buffers at pH 6.8. The solution was filtered and the absorbance was measured spectrophotometrically at 250 nm against phosphate buffer at pH 6.8 as a blank. The amount of drug in one tablet was calculated.

RESULTS AND DISCUSSION

Evaluation parameters

Evaluation of the characteristics of the powder mixture of the Chlorpromazine HCl matrix tablet formulation For each type of formulation, mixtures of Chlorpromazine HCl and other excipients were prepared and evaluated for various parameters such as bulk density, plugging density, compressibility index of Carr, Hausner relationship and rest corner. The apparent density was found in the range of 0.355-0.3850 g / cm3 and the derived density between 0.4101 and 0.4880 g / cm3 indicates that both parameters were within the limits. Using the two density data reported above, the Carr compressibility index was calculated. The compressibility index and the Hausner relationship were found in the range of 7.27-18.42% and 1.053-1.24 respectively, which indicates that all mixtures of powder exhibited excellent to acceptable flow properties. The flow property of all powder mixtures is best explained by the angle of repose. The angle of repose was found in the range of 25.33 to 31.43°. The angle of repose results showed that all the powder mixtures had good to fair flow properties.

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

After compression, several quality control tests were carried out, which demonstrated the following organoleptic properties viz. color, smell and shape. All formulations (F1 to F7) were white, odorless and concave, rounded and flat with a break line on one 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 aim of the present study was to investigate the possibility of supporting the release of Chlorpromazine HCl from the prepared tablet using different concentrations of crosslinking agents and polymers. From the result obtained, the following conclusions can be drawn. Pre-formulation studies, such as angle of repose, bulk density, Haunser ratio of thread density, and Carr's index of all formulations were found to be within standard limits. The powder mixtures were compressed into tablets and evaluated for post- compression parameters such as weight, thickness, hardness, friability, and change in drug content. All formulation batches showed acceptable results. In vitro drug release was studied with a USP type II dissolution apparatus in both simulated gastric fluid and intestinal fluid over a 24-hour period. The results showed that formulations containing a higher concentration of HPMC, i.e., F4 (99.54%) and MCC, i.e., F7 (98.78%), maintained drug release for a period of 24 hours.

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