Original Research Article

FORMULATION AND CHARACTERIZATION OF FAST DISSOLVING ORAL WAFERS CHLORTHALIDONE

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ABSTRACT

Hypertension is a highly hazardous disease; it can come at any time in elderly individuals, thus medications are available at all times and can be administered by patients in a very simple manner. To address these issues, formulators have made significant investments in the development of innovative drug delivery systems (NDDS). Fast dissolving wafers are one such method. Being a very useful drug for decreasing hypertension, this work aims at Formulation and Characterization of fast dissolving oral wafers of Chlorthalidone. The formulation & evaluation of oral wafer was performed according to standard protocol. In total nine formulations were created and all were found to be translucent. The thickness found to be ranged from 78±3 µm to 93±4 µm while the weights of formulations found to be varied from 105±5 mg to 117±8mg. The folding endurance was observed to be maximum for F7 which is 195±2 times. The pH ranges of formulations varied from minimum 6.72±0.15 to 6.95±0.14. The % moisture content varied from 2.3±0.4 to 2.9±0.5. The drug content was found to be maximum for F7 which is 99.85±0.25% also, the disintegrating time was observed to be 16±2 second. The *in-vitro* release study of optimized formulation F7 was observed to be 98.85 at 300 seconds. Minor difference was found between evaluated parameters before and after ageing/storage and all was in acceptable limits. Therefore formulation remains stable for sufficient time. Thus, it can be concluded that formulation of F7 have all ideal parameters & can be further implicated for clinical trials.

Keywords: Hypertension, Antihypertensive drugs, Chlorthalidone, Novel drug delivery system, Oral wafer, Fast dissolving

INTRODUCTION

Hypertension (HTN), often known as high blood pressure, is a chronic medical disorder in which the blood pressure in the arteries is increased. Blood pressure is measured in two parts: systolic and diastolic, depending on whether the heart muscle is contracting (systole) or relaxing (diastole). This is equal to the greatest and minimum pressures. At rest, normal blood pressure is 100-140mmHg systolic and 60-90mmHg diastolic. If your blood pressure is frequently at or over 140/90 mmHg, you have high blood pressure (Kearney *et al*., 2004). Primary (essential) hypertension and secondary hypertension are the two types of hypertension. If untreated, hypertension puts strain on the heart, leading to hypertensive heart disease and coronary artery disease. Hypertension is also a key risk factor for stroke, artery aneurysms (such as aortic aneurysm), peripheral arterial disease, and chronic kidney disease. Although dietary and lifestyle adjustments can improve blood

pressure regulation and reduce the risk of health issues, medication treatment is still frequently required in persons for whom lifestyle changes are insufficient or ineffective (Chiang *et al*., 1969; Lionakis *et al*., 2012).

Normally, all medications are delivered orally through the use of water or other liquid carriers. Water may or may not be provided during an emergency (for hypertension patients). Also Nearly 35% of the general population, particularly the elderly and children, suffer from dysphasia or trouble swallowing, resulting in a high rate of noncompliance and unsuccessful therapy. To address these issues, formulators have made significant investments in the development of innovative drug delivery systems (NDDS) that improve drug molecule safety and efficacy while also improving patient compliance (Laurent,2017; Vikas *et al*., 2011). Fast dissolving wafers are one such method. which disintegrate or dissolve in saliva and are swallowed without water as tablet disintegrate in mouth, this could boost the therapeutic action of medicine by pregastric absorption from the mouth, pharynx, and oesophagus. By avoiding first pass hepatic processing, this increases bioavailability. Wafers, as innovative drug delivery vehicles, have higher patient compliance and may offer improved biopharmaceutical characteristics, efficacy, and safety when compared to standard dosage forms. Because of the availability of modern technology paired with well-established market acceptance, the Flash release wafer appears promising. The future prospects for advancements in quick dissolving medication delivery systems are promising (Nagesh *et al*., 2016; Costa *et al*., 2019).

Chlorthalidone is a thiazide-like diuretic that is used to treat hypertension as well as to manage edoema induced by illnesses such as heart failure or renal impairment. Chlorthalidone lowers blood pressure and edoema by decreasing water absorption from the kidneys by inhibiting the Na+/Cl symporter in the kidney's distal convoluted tubule cells. The precise mechanism of chlorthalidone's antihypertensive impact is unknown; nevertheless, it is believed that enhanced diuresis results in decreased plasma and extracellular fluid volume, decreased cardiac output, and therefore total blood pressure reduction (Roush *et al*., 2013; Filipova *et al*., 2020). Being a very useful drug for decreasing hypertension, this work aims at Formulation and Characterization of fast dissolving oral wafers of chlorthalidone.

MATERIALS AND METHODS

Chemicals

HPMC K4, Carbopol, PEG-400, SSG, CCS, CP, Mannitol, Citric acid, DM water were obtained from S.D Fine chemicals Mumbai. All chemicals & reagents are of standard laboratory grade.

Formulation development of oral wafers of Chlorthalidone

Chlorthalidone containing fast dissolving wafers were fabricated by the solvent casting method.

Evaluation of prepared wafers

Thickness

Three random wafers were selected from each batch and the thickness was measured at three different places using a vernier caliper (Sushmitha *et al*., 2014).

Weight uniformity

For each formulation, three randomly selected patches were used. For weight variation test, 10 wafers from each batch were weighed individually by digital electronic balance and the average weight and relative standard deviation was calculated (Garsuch and Breitkreutz, 2009).

Surface pH Determination

The surface pH of fast dissolving wafers was determined in order to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may cause irritation to the oral mucosa, it is important to keep the surface pH as close to neutral as possible (Mehravaran *et al*., 2022). The wafer to be tested was placed in a petridish and was moistened with 0.2 ml of distilled water. The electrode of pH meter (Electronic india) was placed on the surface of wafer to determine the surface pH.

Folding Endurance

This was determined by repeatedly folding one wafers at the same place until it broke. The number of times the wafers could be folded at the same place without breaking cracking gave the value of folding endurance.

Percentage of Moisture Content

The wafers were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs. Individual wafers were weighed repeatedly until they showed a constant weight.

Drug Content Analysis

The patches (n=3) of specified area were taken into a 10 ml volumetric flask and dissolved in methanol and volume was made up with 10 ml methanol. Subsequent dilutions were made and analyzed by UV spectrophotometer at 256nm.

Disintegrating time

The most important criteria of present work are to that dosage form should be dissolved within few seconds. The incorporation of polymers to minimizes the disintegrating time. In vitro disintegration time was determined by placing the wafer in a petridish containing 10ml distilled water with swirling every 10 sec. The time at which the wafer disintegrated was noted

In vitro dissolution study

The *in vitro* dissolution test was performed using the USPXXX dissolution apparatus II (Paddle type) (Boateng *et al.,* 2012). The dissolution studies were carried out at $37\pm0.5°C$; with stirring speed of 50 rpm in 900 ml phosphate buffer (pH 6.8). Wafers size required for dose delivery (2.5×2.5 cm^2) was used. Five ml aliquot of dissolution media was collected at time intervals of 1, 2, 5, 10 and 15 minutes and replaced with equal volumes of phosphate buffer (pH 6.8). The collected samples were filtered through 0.45 μm membrane filter and the concentration of the dissolved Chlorthalidone was determined using UV-Visible spectrophotometer at 256nm. The results were presented as an average of three such concentrations.

Stability studies

Stability studies were carried out with optimized formulation which was stored for a period of one, two and three months at $40\pm2°C$ temperature and $75\pm5\%$ relative humidity for a period 3 months. The % Assay of formulation was determined by U.V.

spectrophotometer using calibration curve method. The % assay of wafers was found to slightly decrease at higher temperature.

Table 1: Selection and Optimization of Wafers Forming Agents

Name of ingredients (mg) (mg for 12 strips)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Chlorthalidone	75	75	75	75	75	75	75	75	75
HPMC K4	50	100	150	-	-	-	25	50	75
Carbopol	-	-	-	50	100	150	25	50	75
PEG-400	50	50	50	50	50	50	50	50	50
SSG	25	50	100	-	-	-	-	-	-
CCS	-	-		25	50	100	-	-	-
CP	-	-	-	-	-	-	25	50	100
Mannitol	10	10	10	10	10	10	10	10	10
Citric acid	10	10	10	10	10	10	10	10	10
DM water qs to (ml)	30	30	30	30	30	30	30	30	30

Dose calculations

- Width of the plate = 5cm

- Length of the plate = 12cm

- No. of 2.5 x 2.5 cm2 wafers present whole plate = 12

- Each wafers contains 50 mg of drug.

- 12 no. of wafers contains mg of drug? = 6.25×12 = 75mg

- The amount of drug added in each plate was approximately equal to 75mg.

Table 2: Results of Evaluation of prepared Wafers

Formulation code	General Appearance	Thickness* in μm	Weight* mg
F1	Translucent	78±3	110±5
F2	Translucent	90±5	115±3
F3	Translucent	93±4	113±2
F4	Translucent	82±3	114±4
F5	Translucent	86±2	105±5
F6	Translucent	92±2	116±7
F7	Translucent	85±1	117±8
F8	Translucent	87±3	113±5
F9	Translucent	89±2	117±6

*Average of three determinations (N=3)

Table 3: Result of surface pH determination, folding endurance, percentage of moisture content

Formulation code	Folding endurance* (Times)	Surface pH Determination	Percentage of Moisture Content*
F1	155±5	6.72±0.15	2.3±0.3
F2	162±7	6.85±0.20	2.9±0.5
F3	178±8	6.95±0.14	2.7±0.2
F4	169±6	6.74±0.12	2.3±0.4
F5	144±5	6.45±0.13	2.6±0.5
F6	170±3	6.76±0.14	2.8±0.8
F7	195±2	6.81±0.15	2.9±0.4
F8	180±1	6.74±0.17	1.8±0.3
F9	174±4	6.66±0.11	2.7±0.3

Table 4: Drug content analysis and disintegrating time

Formulation code	Drug content analysis (%)	Disintegrating time (Sec.)
F1	97.85±0.25	25±5
F2	98.56±0.32	30±3
F3	98.74±0.15	35±5
F4	98.65±0.20	22±4
F5	97.85±0.10	29±3
F6	98.85±0.22	30±2
F7	99.85±0.25	16±2
F8	98.74±0.23	26±4
F9	98.65±0.15	20±3

Table 5: Results of *in-vitro* release study of optimized formulation F7

S. No.	Time (Sec.)	Percentage cumulative drug release
1.	60	55.65
2.	120	75.65
3.	180	88.98
4.	240	93.32
5.	300	98.85

RESULTS AND DISCUSSION

In total nine formulations were created and all were found to be translucent. Some physical parameters like thickness & weight was separately evaluated. The thickness found to be ranged from 78±3 µm to 93±4 µm while the weights of formulations found to be varied from 105±5 mg to 117±8mg. The number of times the film can be folded at the same area without breaking determines the value of folding endurance. The folding endurance was observed to be maximum for F7 which is 195±2 times. The pH of the film must be checked since the surface pH of a wafer can damage the oral mucosa. The pH of the wafer's surface needs to be around 7 or neutral. The pH ranges of formulations varied from minimum 6.72±0.15 to 6.95±0.14. The % moisture content varied from 2.3±0.4 to 2.9±0.5. The drug content was found to be maximum for F7 which is 99.85±0.25% also, the disintegrating time was observed to be 16±2 second. The *in-vitro* release study of optimized formulation F7 was observed to be 98.85 at 300 seconds. Minor difference was found between evaluated parameters before and after ageing/storage and all was in acceptable limits. Therefore formulation remains stable for sufficient time. Minor difference was found between evaluated parameters before and after ageing/storage and all was in acceptable limits. Therefore formulation remains stable for sufficient time.

CONCLUSION

Wafers as an orodispersible film have carved out their own niche in the recent trend towards more palatable dosage forms, and have met rising demand. Because of their high absorption and bioavailability, wafers are used to supplement oral quick dissolving films. Due to its compatibility and pleasant flavour, it is popular among people of all ages, but especially among the elderly and children.

Chlorthalidone, an anti-hypertension medication, was used for the production of oral wafers. The solvent casting method was used to successfully make chlorthalidone oral wafers. HPMC K4 polymers were employed in the preparation of flash release oral wafers. In-vitro drug dissolution and drug release kinetics of Chlorthalidone were 99.850.25 at 300 seconds based on this physiochemical evaluation. The evaluation test for Chlorthalidone wafer suggests that it is promising to be produced as oral wafers with the aforementioned excipients, which can boost diffusion, so affecting release and thus bioavailability, and may have an impact on its bioavailability.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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