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FORMULATION AND EVALUATION OF FAST DISSOLVING ORAL FILM OF CHLORZOXAZONE USING DIFFERENT FILM FORMING AGENTS

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Abstract:
Muscle spasm needs prompt relief of symptoms. Chlorzoxazone is a centrally muscle relaxant. Which are having shorter half life (1.1hour) with the dose administration of 3-4 times a day. Oral film of chlorzoxazone quickly disintegrates and dissolves and can be administered without water, making them particularly suitable for geriatric patients and found faster action. Fast dissolving oral films (FDOFs) have gained popularity not only in breath strips but also in personal care, food drug delivery markets. The aim of present work is to formulate and evaluate fast dissolving oral films of chlorzoxazone to improve water solubility, dissolution rate, oral bioavailability and reduction of first pass metabolism and increase patient's compliance. Oral fast dissolving films prepared by solvent casting method using water and 95% ethanol as solvents and gelatin, xanthan gum, gum acacia as film forming polymer. Superdisintegrants such as croscarmellose sodium (CCS) was incorporated to achieve the aim. The prepared films were evaluated for the drug content, weight variation, film thickness, folding endurance, disintegration time, percentage of moisture content and in vitro dissolution studies and taste mask studies on healthy human volunteers. Among all, the formulation F6 was found to be best formulation which releases 98.85±0.25% of the drug within 360sec and disintegration time is 10±5sec. which was significantly high when compared to other formulation.

Keywords: *Chlorzoxazone, Fast dissolving oral film, Bioavailability, Mechanical properties*

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INTRODUCTION:

Rapidly dissolving or quick dissolving dosage forms have acquired great importance in the pharmaceutical industry due to their unique properties and advantages [1, 2]. These systems either dissolve or disintegrate within a minute, on contact little quantity of water or by chewing. This delivery system consists of a thin film, which is simply placed on the patient's tongue or mucosal tissue, instantly wet by saliva; the film rapidly dissolves. Then it rapidly disintegrates and dissolves to release the medication for oral mucosal absorption [3, 4]. The major portion of the active ingredient is swallowed orally along the saliva and absorption takes place in the gastrointestinal tract subsequently making them particularly suitable for pediatrics and geriatric patients. The fast dissolving films were introduced in 1970's as an alternative to the conventional tablet and capsule which require swallowing of the dosage form. The rapidly dissolving dosage forms are referred by various names by researchers like quick disintegrating, orally disintegrating, mouth dissolve or melt in mouth dosage forms [5, 6]. These dosage forms offer specific advantages including no need of water for disintegration, accurate dosing, ease of transport, handling, acceptable taste, rapid onset of action and patient compliance [7, 8]. The trans mucosal deliveries of metformin, dexamethasone and levocetrizine hydrochloride have proved their enhanced bioavailability over the conventional formulations [9, 10]. Solvent casting was proved to be reliable technique for the manufacturing of fast dissolving films. The film strips prepared by this method undergo instantaneous disintegration upon placing in buccal/oral cavity. The plasticizers present in fast dissolving films formulation, reduce the glass transition temperature and thereby enabling desired film qualities [11]. Muscle spasm is a painful reflex contraction of muscle that can cause involuntary movement and interfere with muscle function, causing defacement. It can be caused by musculoskeletal conditions or by neurological conditions associated with upper motor neuron lesions (spasticity) [12]. Common skeletal muscle relaxants have been approved for either treatment of spasticity or for treatment of musculoskeletal conditions. Only baclofen, dantrolene and tizanidine are approved by FDA for the treatment of spasticity, but carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol and orphenadrine have been approved for treatment of musculoskeletal disorders [13]. Chlorzoxazone is a centrally acting musculoskeletal relaxant with sedative properties. Its chemical name is 5-chloro-2(3H)-benzoxazolone, with low solubility in water. After oral administration, Chlorzoxazone is completely absorbed and is rapidly metabolized in the liver to 6-hydroxychlorzoxazone which has little or no muscle relaxant activity when tested in mice and rats [14]. Chlorzoxazone inhibits muscle spasm by exerting an effect primarily at the level of the spinal cord and subcortical areas of the brain. Its effect begins within an hour after an oral dose and lasts for 3-4 h. The usual initial oral dose is 500 mg three or four times daily; though the dose can often be reduced subsequently to 250 mg three or four times daily. Chlorzoxazone is usually given with analgesics in compound preparations. The most common side effects of CLZ are drowsiness, dizziness and headache [12]. Chlorzoxazone belongs to biopharmaceutics classification (BCS) class II, where its solubility is poor in gastrointestinal fluid and showing good permeability. Low solubility and dissolution rate of poorly water-soluble drugs make them suffer from limited clinical effect [15]. The objective of the present research work was to develop fast dissolving oral films of chlorzoxazone disintegrating within 10s to enhance the convenience of administration to the patients to improve compliance. The formulation developed was simple, easy to prepare and economical with great applicability and also giving faster *in vitro* drug dissolution rate as compared to the commercially available immediate release tablets.

MATERIALS AND METHODS:

Materials

Chlorzoxazone was obtained as a gift sample from Hetero Drugs Ltd Hyderabad. HPMC was procured from Qualikems fine chem. Pvt Ltd Vadodhara. Xanthan gum, gelatin, gum acacia, croscarmellose sodium was obtained from S.D fine chemicals limited, Mumbai. Citric acid, ethanol was obtained from Loba Chemical Pvt Ltd (Mumbai, India). Hydrochloric acid, KH_2 PO_4, NaoH was obtained from S. D. Fine Chem. Ltd., Mumbai. All other chemical were purchased from Hi Media, Mumbai. Double distilled water was prepared freshly and used whenever required. All the chemicals used in this work were of analytical grade.

Formulation development of oral film of chlorzoxazone

Solvent casting technique

Drug (Chlorzoxazone) containing fast dissolving films were fabricated by the solvent casting method [16]. The optimized amount of xanthan gum, gelatin, gum acacia was dissolved in 5ml of water and stirrer continuously for 1 hour, optimized amount of Plasticizer and drug were dissolved in 95% ethanol and then added to the polymeric solution, the optimized amount of drug was dissolved in 2ml of

water and kept on sonication for proper dispersion. Polymeric solution was stirred for 30 min using magnetic stirrer and was kept in undisturbed condition till the entrapped air bubbles were removed. The aqueous solution was casted in a glass moulds having 2.5 x 2.5 cm * 10 films area and was dried at controlled room temperature (25°-30°C, 45 %RH) as well as at increased temperature (microwave oven). The film took approximately 48 hr to dry at controlled room temperature. The dried film was carefully removed from the glass plates and was cut into size required for testing. The films were stored in air tight plastic bags till further use. The compositions of the formulations were shown in table 1.

Table 1: Selection and optimization of film forming agents

Name of ingredients (mg for 12 strips)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Chlorzoxazone	600	600	600	600	600	600	600	600	600
Xanthan gum	100	200	300	100	200	300	100	200	300
Gelatin	25	50	100	25	50	100	-	-	-
Gum acacia	10	20	30	-	-	-	10	20	30
Cross carmellose sodium	-	-	-	25	50	75	25	50	75
Methyl Paraben	20	20	20	20	20	20	20	20	20
Aspartame	20	20	20	20	20	20	20	20	20
Citric acid	50	50	50	50	50	50	50	50	50
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 film present whole plate = 12
- Each film contains 150 mg of drug.
- 12 no. of film contains mg of drug? = 50×12 = 600mg
- The amount of drug added in each plate was approximately equal to 600mg.

Evaluation

The formulations were evaluated by the following tests [17-21].

Thickness

Randomly 10 films were selected and thickness was measured using vernier calliper at three different places.

Weight variation

For each formulation, three randomly selected patches were used. For weight variation test, 10 films from each batch were weighed individually by digital electronic balance and the average weight was calculated.

Folding endurance

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

Percentage of moisture content

The films were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight.

$$\text{Percentage of Moisture Content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \text{x } 100$$

Surface pH determination

The surface pH of fast dissolving film 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. 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.

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 278nm.

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). The dissolution studies were carried out at 37±0.5°C; with stirring speed of 50 rpm in 900 ml phosphate buffer (pH 6.8). Film 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 Chlorzoxazone was determined using UV-Visible spectrophotometer at 278nm. 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±2°C temperature and 75±5% relative humidity for a period 3 months. The % Assay of formulation was determined by U.V. spectrophotometer using calibration curve method. The % assay of film was found to slightly decrease at higher temperature.

RESULTS AND DISCUSSION:

λ_{max} of chlorzoxazone was found to be 228 nm in 0.1 N HCl solution by using U.V. spectrophotometer (Labindia-3000+). The calibration curve of chlorzoxazone was found to be linear in the concentration range of 5-25µg/ml at 278nm. The general appearance, weight variation and thickness of all the films were within acceptable limits table 2. The results for folding endurance, surface pH determination and % of moisture were shown in table 3. Surface pH value of optimized formulation (F6) was 6.8±0.4 and folding endurance was more than 220. The assay values of all the formulations were ranging from 97.89±0.32 to 99.85±0.41%. The disintegration time was ranging between 10±5 to 22±6sec. The final formulation shows better drug release (98.85±0.25%) compared to other formulation within 360 sec (table 5). The cumulative percentage (%) drug release profile and the assay of the F6 formulation films indicates that the drug remain stable under the ASC without any significant change in its release profile and the drug content. From the stability studies it was clearly observed that the drug showed good stability after subjecting to accelerated stress conditions and the polymers shown significantly compatibility with the drug.

Table 2 Result of general appearance, thickness and weight variation

Formulation code	General Appearance	Thickness* in µm	Weight* mg
F1	Translucent	55.3±0.2	82±3
F2	Translucent	62.2±0.3	86±4
F3	Translucent	65.5±0.2	89±2
F4	Translucent	58.8±0.1	91±5
F5	Translucent	62.2±0.5	93±6
F6	Translucent	64.5±0.4	95±4
F7	Translucent	63.3±0.6	89±5
F8	Translucent	65.4±0.3	91±6
F9	Translucent	63.4±0.5	94±2

***Average of three determinations (N=3)**

Table 3 Result of folding endurance, surface pH determination & % of moisture content

Formulation code	Folding Endurance* (Times)	Surface pH Determination	Percentage of Moisture Content*
F1	125±4	6.6±0.2	2.23±0.15
F2	136±6	6.7±0.3	2.45±0.23
F3	142±2	6.5±0.1	2.65±0.25
F4	135±4	6.7±0.2	2.41±0.14
F5	165±2	6.6±0.5	2.12±0.26
F6	220±3	6.8±0.4	1.75±0.32
F7	136±2	6.7±0.3	1.92±0.35
F8	145±4	6.5±0.4	2.23±0.41
F9	168±5	6.7±0.3	2.41±0.25

***Average of three determinations (N=3)**

Table 4: Drug content analysis and disintegrating time

Formulation code	Drug content analysis (%)	Disintegrating time (Sec.)
F1	98.45±0.25	23±4
F2	97.89±0.32	20±5
F3	98.87±0.45	22±6
F4	99.05±0.36	18±4
F5	98.74±0.14	15±7
F6	98.65±0.25	10±5
F7	99.85±0.41	18±3
F8	98.45±0.32	19±2
F9	98.69±0.15	17±7

Table 5: Results of *In-Vitro* release study of optimized formulation F6

S. No.	Time (Sec.)	Percentage cumulative drug release
1.	60	36.65±0.45
2.	120	49.95±0.32
3.	180	55.65±0.25
4.	240	69.98±0.36
5.	300	83.32±0.41
6.	360	98.85±0.25

CONCLUSION:

From present investigation it can be concluded that oral fast dissolving films are superior in drug release. The films prepared by xanthan gum and gelatin had shown good mechanical strength, drug release, disintegration time and stability. F6 formulation is considered as the best according to the obtained results with less disintegrating time and complete drug release in 360sec. Percent drug release and disintegration time was taken as responses for study which were found within the accepted ranges. As the concentration of CCS was increased, both the disintegration and the drug release rates increased. The disintegration and release rates were found to be faster for films prepared with lowest concentration of xanthan gum along with maximum concentration of superdisintegrants. Chlorzoxazone administered in the form of fast dissolving films will be potential novel drug dosage form for pediatric, geriatric and also for general population by providing faster release and better patient compliance.

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