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Original Article

Formulation and evaluation of orodispersible films of atropine sulfate for sialorrhea

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ABSTRACT

Excess oral secretions or sialorrhea is a common problem affecting children and adults with neurological disorders, as well as those approaching the end of life because of a variety of underlying illnesses. Systemic anticholinergic medications are often prescribed in an attempt to improve quality of life and reduce complications. Atropine is a racemic mixture of d-hyoscyamine and l-hyoscyamine. It is a competitive antagonist of the muscarinic receptors, thereby inhibiting the effect of acetylcholine, a major neurotransmitter of the parasympathetic nervous system, also innervating the submandibular glands. It blocks the muscarinic receptors in the salivary glands and leads to reduced saliva production. Orodispersible films are solid dosage forms, which disintegrate or dissolve within a minute when placed in the oral cavity. In the current study atropine sulphate orodispersible films are formulated by solvent casting method using pullulan and HPMC E 15 polymer combination. The prepared formulations were evaluated using different parameters and they exhibited acceptable physical characteristics with good flexibility, folding endurance, tensile strength and percentage elongation. All the formulations quickly disintegrated and released the drug. Therefore, orodispersible films can be considered potentially suitable for the immediate release of drug atropine sulfate for reducing excess of salivation.

Key Words: Orodispersible films, atropine sulfate, sialorrhea, fast disintegration

INTRODUCTION

In modern era, the development of novel delivery system for oral route has grabbed a lot of attention due to its patient compliance. Delivery through buccal route was considered as one of the important alternatives to administer the loaded drug through oral route, as it was considered as the most convenient, easiest, and the fastest route of drug absorption.[1]

In the recent years, many of the pharmaceutical groups are focusing their research on rapid dissolving technology. The main advantage of this

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technology is the administration to paediatric and geriatric patient population where the difficulty of swallowing larger oral dosage forms is eliminated orally. [2] Due to the fact that the active substance can be administered in a solid form, but without the need to swallow them with water, they are a good alternative as oral drugs for special patient groups, e.g., geriatric or paediatric patients and patients with dysphagia. In this technology, the film is hydrated by saliva when placed on the tongue and disintegrates rapidly, releasing the active substance for local (oromucosal) or systemic (gastrointestinal) absorption, without the risk of choking. This does not mean, however, that the drug itself dissolves quickly, and for poorly soluble drugs, it can be still a challenge to obtain fast dissolution and absorption. [3] Typical film has thickness 1 to 10mm and its surface area can be 1 to 20 cm^2. It is easy to handle and apply due to its low dry tack. The typical disintegration time, which is defined as the time at which the film begins to break when brought into contact with water, is only 5 to 10 seconds for the film with a thickness of 2 mm. The dissolving time, which is defined as the time at which not less than 80% of the tested film is dissolved in aqueous media, is around 30 seconds for film with a thickness of 2 mm. [4]

The management of excess oral secretions is a challenge in adults and children who are living or dying with this problem. Regardless of the age or the underlying condition, the cause of sialorrhea is the inability to handle one's own saliva, rather than hypersalivation. Yet, because the cause is often irreparable, treatment is aimed at reducing the production and consistency of saliva to a more manageable state.

Atropine (DL-hyoscyamine) is an anticholinergic medication that reduces saliva production by blocking the muscarinic (M3) receptor sites on the salivary glands.[5] Atropine is a racemic mixture of d-hyoscyamine and l-hyoscyamine, where the latter is responsible for the most of the physiological effects. It is a competitive antagonist of the muscarinic receptors, thereby inhibiting the effect of acetylcholine, a major neurotransmitter of the parasympathetic nervous system, also innervating the submandibular glands. The effect of atropine on sialorrhea can theoretically be explained by its action as a competitive antagonist of acetylcholine on the muscarinic receptors in the salivary glands.[6] H. Diamant and M. Feinmesser conducted a comparative study on the efficiency of atropine as an antisialagogue with l-hyoscyamine (bellafoline), scopolamine butyl bromide (buscopan) and oxyphenonium (antrenyl) and reported that atropine has a very good antisialogogue action in doses which produce no toxic effects.[7]

Orodispersible films (ODFs), a relatively new dosage form for oral route of administration, are postage stamp-sized strips of thin polymeric films formulated to disintegrate or dissolve almost instantaneously when placed onto the tongue. They are used in case of patients who have difficulty in swallowing such as elderly, pediatric patients, and others suffering from mental illness and developmental disorders. The drug in ODFs is absorbed through the oral mucosa, which make drugs enter the systemic circulation without undergoing first-pass hepatic metabolism. [8]

A fast-dissolving drug delivery system (FDDDS) is the most convenient mode of administering drugs to overcome problems related to swallowing difficulties. These delivery systems dissolve or disintegrate in the mouth rapidly, without requiring any water to aid in swallowing. Dissolution within oral cavity also permits intra-oral absorption, thus bypassing first-pass effects. FDDDS offer advantages such as disintegration without water, rapid onset of action, ease of transportability, ease of handling, pleasant taste, and improved patient compliance.[9]

Therefore, in the present work an attempt was made to formulate orodispersible films of atropine sulfate for immediate release of drug for reducing excess of salivation.

MATERIALS AND METHODS

Materials: Atropine sulfate was procured from Yarrow Chem, Mumbai, India. Pullulan, hydroxy propyl methyl cellulose (HPMC) E15, and poly ethylene glycol (PEG) was purchased from Loba Chemicals, Mumbai. Ethanol was purchased from Hi Media Laboratory Pvt. Ltd, Mumbai, India. All the chemicals/reagents were used of analytical grade

Formulation of orodispersible films of atropine sulfate: The orodispersible films of atropine sulfate were formulated by solvent casting method. [10, 11]

Preparation of casting solution: The casting solution was prepared using the polymers pullulan and HPMC E15 in combination. The weighed quantity of drug (8.75 mg), and polymers (50-150 mg) were dissolved in 5ml of water. Aspartame (40 mg) was dissolved in 3ml of ethanol in a beaker. Both the solutions were mixed and stirred on magnetic stirrer until dissolved. PEG was added as a plasticizer (0.1-0.3 ml). The beaker was covered with an aluminium foil, and allowed to stand overnight to remove air bubbles.

Preparation of orodispersible films: The casting solution (8 ml) was poured into petri plate (70 cm^2) and kept aside to allow for controlled evaporation of the solvent. The dried film was removed by peeling and cut into squares with a dimension of 2 × 2 cm (4 cm^2), each film contained 0.5 mg drug and kept in a desiccator over fused calcium carbonate for 2 days for further drying and wrapped in an aluminium foil.

Evaluation of orodispersible films:

Visual Inspection

The prepared films were visually observed for color, transparency and homogeneity to assess some organoleptic properties.

Thickness

Thickness was measured using vernier calipers. The thickness was measured at three locations (one at center and four corners of the film), and the mean thickness was calculated. Samples with air bubbles, nicks and having mean thickness variation of greater than 5% are excluded from analysis.[12]

Weight Variation

Films 2 × 3 cm^2 in size were weighed on an electronic balance. The measurements were carried out in triplicates.[13]

Folding Endurance

This gives an indication of the brittleness of the film. The film was repeatedly folded in the same spot until it broke. The folding endurance was taken as a function of the number of times the film is folded before breakage. The experiment was done in triplicates and the mean ±SD was calculated.[13]

Tensile strength: Tensile testing was conducted using the modified method. The film was cut into 30 × 20 mm strips. Each test strip was stick on the surface of Glass slide with the help of Feviquick. Initial grip separation was 20 mm. The test was considered concluded when the film breaks. Tensile strength was computed with help of load require to break the film and cross-sectional area to evaluate tensile properties of the films. Tensile strength is the maximum stress applied to a point at which the film specimen breaks and can be calculated by dividing the maximum load by the original cross-sectional area of the specimen and it was expressed in force per unit area (MPa). Typical tensile strength for film is1.80± 0.20MPa. [2]

Tensile strength (N/mm2) = breaking force (N)/cross-sectional area of sample (mm2)

Percentage Elongation (% E)

When stress is applied the film, sample stretches and is referred to as strain. Strain is basically the deformation of the film divided by the original dimension of the film. Generally, elongation of the film increases as the plasticizer concentration increases

Percentage elongation was calculated by measuring the increase in length of the film after tensile strength measurement by using the following formula;

$$\text{Percentage elongation} = \frac{[L - L_0] \times 100}{L_0}$$

where L = final length and L_0 = initial length.

The estimations were carried out in triplicate.[14]

Disintegration time: The in *vitro* disintegration time of the formulations was determined by petri dish method. About, 2 ml simulated saliva (pH 6.8) was placed in a clean dry petri dish and the film (2 X 2 cm) was placed on its surface. The time required for the complete disintegration of the film was noted as the disintegration time. The test was performed on three strips of each formulation batch and mean ± SD was calculated.[10]

Drug content uniformity: The optimized film of specific area (2 X 2 cm) was cut and transferred to a graduated flask containing 100 ml of simulated salivary fluid pH 6.8 and stirred on a magnetic stirrer for 4 h. The solution was then filtered using a Whatman® filter paper. The filtered solution was diluted using the simulated salivary fluid. The absorbance will be measured using UV spectrophotometer (V-630, JASCO, Japan) at λ_{max} 220 nm. [15]

***In vitro* drug release:** The optimized films of known weight and dimension (2 X 2 cm) were placed in a beaker containing 20ml of simulated salivary fluid (pH 6.8) as the dissolution medium maintained at 37±0.5°C. The medium was stirred at 100 rpm. Aliquots (5 ml) of samples were taken at 5sec time intervals, and the same volume of fresh phosphate buffer was replaced. Samples were filtered, diluted suitably and analysed using UV/Visible spectrophotometer (V-630, JASCO, Japan) at λ_{max} 220 nm. The cumulative percentage drug release was calculated and plotted against time (sec). [15]

RESULTS AND DISCUSSION

Visual Inspection: The orodispersible films formulated with different polymer concentration were found to be homogenous, transparent, flexible, colourless, non-sticky, smooth in texture and elegant in appearance.

Thickness: As the concentration of polymer and plasticizer increased the thickness of the film found to be increased. The film's thickness appears ideal and suitable for oral administration.

Weight variation: All the prepared formulations were uniform in weight with no significant difference in the weight of the individual

formulations from the average value. Weight variation was found to be in the range of 28.52 ± 0.05 to 39.51 ± 0.09 mg for films prepared.

Folding Endurance: The folding endurance test is generally used to indicate the capacity of the films to sustain mechanical handling as well as pliability during the use in oral cavity. The folding endurance of the films were found to be in the range of 242 ± 2 to 270 ± 6. It was observed that the folding endurance of the films increased with increase in the concentration of polymer and plasticizer. The flexibility of the films increased with increase in folding endurance.

Tensile strength: The tensile strength of the film is important to resist the mechanical movements that occur during the packing, storage and shipping of the films. The addition of HPMC and pullulan adds supporting strength to the film. The tensile strength of the formulations F1, F2, F3 and F4 were found to be 1.78 ± 0.57, 1.95 ± 0.43, 2.01 ± 0.15, 2.23 ± 0.24 M Pa respectively.

Percentage elongation: The percentage elongation of films was determined and results are tabulated in the table no. 2. The films showed high percentage elongation and percentage elongation was found to increase with the increase in polymer concentration.

Disintegration time: The formulations F1, F2, F3 and F4 showed disintegration time of 12 ± 2, 24 ± 1, 14 ± 2 and 10 ±1 seconds respectively. In the US Food and Drug Administration's (FDA)-Centre for Drug Evaluation and Research (CDER) guidelines, the disintegration limit for fast dissolving oral films is mentioned as 30 sec or less, all four films showed the disintegration time within 30 sec.

Drug content uniformity: The percentage drug content in various formulations ranged from 83.93 % – 98.7 and the drug content was found to be in the limit.

***In vitro* drug release:** The formulations were subjected to *in vitro* drug release studies and the formulations F1, F2, F3 and F4 showed cumulative drug release of 80.2, 82.5, 92.3 and 93.7 respectively at the end of 400 sec. The fast drug release may be because of the faster disintegration and dissolution of the films in the medium. Furthermore, as the concentration of the polymer increased, the drug release was found to be decreased due to increase in the time required for wetting and dissolving the drug molecules present in the polymer matrices.

CONCLUSION

In the present research work orodispersible films of atropine sulfate were formulated by solvent casting method using pullulan and HPMC E 15 polymer combination for the treatment of sialorrhea. The prepared formulations were evaluated using different parameters and they exhibited acceptable physical characteristics with good flexibility, folding endurance, tensile strength and percentage elongation. All the formulations quickly disintegrated and released the drug. Therefore, orodispersible films can be considered potentially suitable for the immediate release of drug atropine sulfate for reducing excess of salivation.

Table 1: Composition of orodispersible films

Formulation code	API (mg)	Pullulan (mg)	HPMC E 15 (mg)	PEG 400 (ml)	Aspartame (mg)	Ethanol (ml)
F1	0.5	50	50	0.1	40	3
F2	0.5	100	100	0.2	40	3
F3	0.5	150	150	0.3	40	3
F4	0.5	200	200	0.4	40	3

Table 2: Evaluation parameters of orodispersible films

Formulation code	Thickness* (mm) (Mean ± SD)	Weight variation* (mg) (Mean ± SD)	Folding endurance* (Mean ± SD)	Tensile strength* (M Pa) (Mean ± SD)
F1	0.25 ± 0.05	28.52 ± 0.05	242 ± 2	1.78 ± 0.57
F2	0.27 ± 0.02	32.74 ± 0.03	261 ± 3	1.95 ± 0.43
F3	0.28 ± 0.01	35.34 ± 0.12	262 ± 5	2.01 ± 0.15
F4	0.31 ± 0.06	39.51 ± 0.09	270 ± 6	2.23 ± 0.24

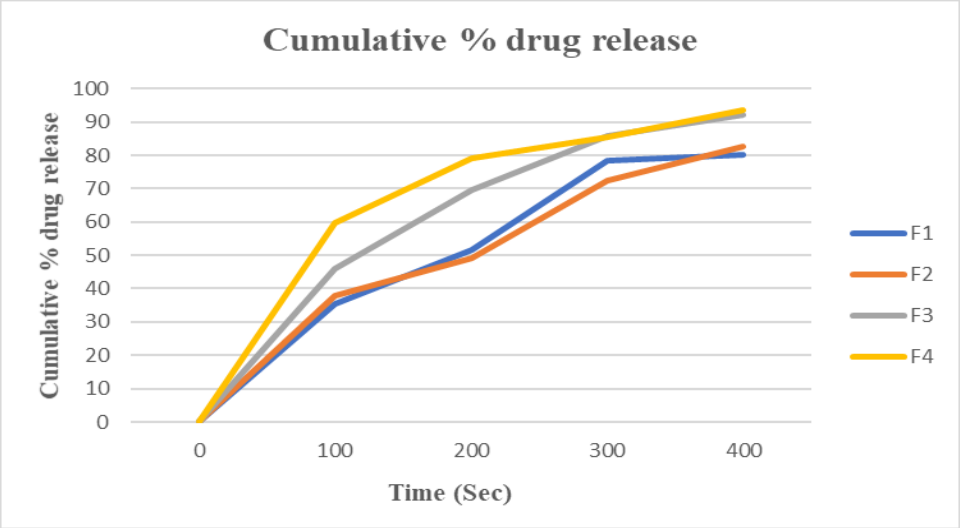
*Each reading is an average of 3 determinations

Table 3: Evaluation parameters of orodispersible films

Formulation code	Percentage elongation*	Disintegration time* (sec)	Drug content uniformity* %	% Cumulative drug release*
F1	16.66 ± 3.67	12 ± 2	83.93 ± 0.28	80.2 ± 0.52
F2	25.56 ± 1.76	24 ± 1	85.62 ± 0.34	82.5 ± 0.61
F3	29.56 ± 2.34	14 ± 2	85.73 ± 0.15	92.3 ± 0.15
F4	33.33 ± 2.58	10 ± 1	98.7 ± 0.32	93.7 ± 0.35

*Each reading is an average of 3 determinations

Figure 1: Cumulative percentage of drug release



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