



Development, Formulation and Evaluation of Atomoxetine Oral Films

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Abstract:

Fast-dissolving drug delivery system offers solution for the problems related to patient compliance especially in the case of geriatric and paediatric population. Atomoxetine is a selective nor epinephrine re-uptake inhibitor. It is used for the treatment of attention-deficit hyperactivity disorder (ADHD). The objective of formulating atomoxetine oral films is to provide rapid dissolution of drug and absorption which may produce the rapid onset of action and also to improve the bioavailability of the drug. Oral films were developed and prepared by solvent evaporation method. The film forming agent used was hydroxypropyl methylcellulose (HPMC) and propylene glycol as a plasticizer. A standard calibration curve was established with the maximum absorption at 269 nm. Further the evaluation of the film was done through a series of tests like thickness, weight variation, *in vitro* dispersion time and pH, drug content determination and drug – excipient compatibility by FT-IR. The mechanical properties of the developed films (tensile strength, % elongation, folding endurance) were also found to be in acceptable limits. Hence, atomoxetine oral dispersing film was formulated and evaluated which results in the development of the product with higher efficacy and bio availability.

Keywords: Atomoxetine, hydroxypropyl methylcellulose, *in vitro* dispersion, and oral films.

INTRODUCTION

Transmucosal delivery was a logical progression. The Quick-Dis™ is a thin film for oral mucosal delivery that overcomes the shortfalls of conventional fast-dissolving intraoral tablets⁽¹⁾. This unique delivery system holds great promise for use in drug delivery devices designed for application to other moist mucosal surfaces in the body, such as ocular, vaginal, and rectal surfaces⁽²⁾. The thickness of oral dispersible film ranges from 1 to 10 mm and its surface area can be 1 to 20 cm² for any geometry. Its low dry-tack allows for ease of handling and application. At the same time, the rapid hydration rate facilitates an almost immediate softening of the film upon application in the oral cavity. The wet-tack and mucoadhesive properties of the system are designed to secure the film to the site of application. The flexibility and strength of the film may be selected / modified to facilitate automatic rewinding, die cutting, and packaging

during manufacturing. The flexibility and strength are reflected by the tensile strength, elongation, Young's Modulus, bending length, and tear resistance of the film. Literature survey revealed a number of drugs which were being formulated such as taste masked fast disintegrating films of levocetirizine dihydrochloride⁽³⁾, domperidone⁽⁴⁾, dicyclomine⁽⁵⁾, telmisartan⁽⁶⁾, montelukast sodium⁽⁷⁾, ropinirole hydrochloride⁽⁸⁾, antipsychotic drug aripiprazole⁽⁹⁾, diclofenac sodium⁽¹⁰⁾ etc. These drugs involved the use of wide variety of film forming agents like Kollicoat IR or pullulan, HPMC (hydroxypropyl methylcellulose), PVA (polyvinylalcohol), Eudragid RL-100 with glycerol or poly ethylene glycol as a plasticizer.

Atomoxetine (ATMX) is a drug approved for the treatment of attention-deficit hyperactivity disorder (ADHD). It is a selective norepinephrine reuptake inhibitor (NRI). Atomoxetine is designated chemically as (-)-N-methyl-3-phenyl-3-(o-tolyloxy)-propylamine hydrochloride as shown in figure 1.

MATERIALS AND METHODS

Materials

Atomoxetine HCl and Aspartame were received as gift samples from Aurobindo Pharmaceuticals Ltd. (Hyderabad, India). Propylene glycol, Hydroxypropyl Methylcellulose 5 cps and 15 cps, Glycerine, Mannitol, Ethanol were procured from SD Fine Chem. LTD. (Mumbai).

Methods

Buffer preparation

Phosphate buffer with pH 6.8 was prepared by dissolving 0.68 gm of potassium dihydrogen orthophosphate in 25 ml of water, 11.2 ml of 0.2M sodium hydroxide and water sufficient to produce 100 ml. Adjusted the pH if necessary.

Determination of absorption maximum

The required quantity of drug was dissolved in phosphate buffer pH 6.8 to get 10 µg/ml solution which was further diluted with the same and scanned for maximum absorbance in UV spectrophotometer ((UV model 1700, Shimadzu, Japan) between a wavelength range of 200 to 400 nm against phosphate buffer pH 6.8 as blank. In this study, atomoxetine hydrochloride showed a maximum absorbance (λ max) at 269 nm. The value was confirmed by repeating the procedure three times.

Calibration curve of Atomoxetine HCl

The required quantity of drug was dissolved in phosphate buffer pH 6.8 to get a stock solution of 100 µg/ml solution from which a serial dilutions were made in order to get 10 µg/ml, 20 µg/ml, 30 µg/ml, 40 µg/ml, 50 µg/ml, 60 µg/ml, 70 µg/ml, 80 µg/ml, 90 µg/ml of the final solution. The absorbance of these dilute solutions was measured at 269 nm by using double beam U.V spectrophotometer against a blank of phosphate

buffer pH 6.8. The calibration curve of ATMX is shown in Figure 2, and has a regression coefficient of 0.991.

Drug – Excipient compatibility by FT-IR

Atomoxetine HCl, HPMC and combination of both were individually mixed with potassium bromide (KBr) in standard proportions and transparent disk like pellets were prepared and the peaks were observed using FT-IR (Shimadzu, Japan).

Screening of the components for formulation of placebo oral films

HPMC is known for its good film forming properties and has excellent acceptability. Hence, various grades of HPMC namely Methocel E5 and Methocel E15 Premium LV were evaluated as film formers. Propylene glycol and glycerine were evaluated as plasticizers in different compositions. The films were evaluated for imperfections, peelability without rupturing, surface roughness, appearance, drying time and *in vitro* disintegration time. Optimization was further performed for the polymer and plasticizer compositions which showed good film properties like flexibility, less drying time, less dispersion time, sufficient mechanical strength, and easy removal from the base.

Development of oral film

The composition of various formulations is given in Table 1. The polymer was weighed and soaked for half an hour in water and ethanol was added. The polymer solution was kept for stirring and the required amount of drug solution was added. The sweeteners, mannitol and aspartame were added and continued stirring. The plasticizer, propylene glycol was added and stirred. The polymer solution was set aside for half an hour if there were signs of air bubbles. This was done in order to prevent the entrapment of the air in the

films which may lead to distorted look and has variation in the kinetic profile of the drug delivery. For the film formation three types of base was tried i.e., glass petri dish, teflon petri dish and saucers. Film formation was compared in terms of easy removal, uniformity in thickness and the cost of base used.

Table 1: Composition of different mouth dissolving films containing ATMX.

Formulation code	F1	F2	F3	F4
HPMC E ₅ (mg)	200	300	400	500
Atomoxetine HCl (mg)	73	73	73	73
Aspartame (mg)	25	25	25	25
PG (ml)	0.15	0.15	0.15	0.15
Mannitol (mg)	25	25	25	25
Ethanol (ml)	5	5	5	5
Water (ml)	5	5	5	5

Once the solution was free of all the air bubbles the solution was poured on to the glass petri dishes. As the removal of the film was not easy from glass petri dish and when fabricated locally, didn't get uniform thickness, so teflon petri dish was tried. Film was formed and removed easily but teflon petri dishes were expensive and finally, porcelain base (saucer) was tried. Film was removable without any difficulty and these saucers were used to prepare the films as these are cheaper.

The resulting thin film was left to dry by covering it with glass funnels in order to provide complete and proper evaporation overnight.

The resulting oral films were removed from the saucer and packed in aluminium foils which were preserved for further study.

Evaluation of the films

Thickness

The thickness of strip was measured by a micrometer at different locations. This measurement is essential to ascertain uniformity in

the thickness of the film as this thickness is directly related to the accuracy of the dose in the film.

Weight variation

For weight variation test, 3 films from each formulation were weighed individually and the average weight was calculated.

In vitro dispersion time

Dispersion time was performed by placing the film of size 3x3 cm² in the glass petri dish containing 20 ml of water. It was stirred at every 10 s time interval. The time required for the film to disintegrate was recorded and results are expressed as mean of 6 determinations.

Determination of pH

The pH of the film was measured by dissolving 3x3 cm² film in 4 ml of water, using a pH meter.

Drug content determination

Film (3X3 cm²) from each formulation was taken, cut into small pieces and was allowed to dissolve in a 100 ml of phosphate buffer pH 6.8. The solution was filtered, diluted suitably and the absorbance of the solution was measured using UV-Visible spectrophotometer at a wavelength of 269 nm against reference solution consisting of placebo films.

Mechanical properties of the film

The mechanical properties are tensile strength, percentage elongation and folding endurance.

Tensile strength

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks (as shown in figure 5). It is calculated by the applied load at rupture divided by the cross-sectional area of the strip as given in the equation below:

$$\text{Tensile strength} = \frac{\text{Load at failure}}{\text{Strip thickness} \times \text{strip width}} \quad (\text{Eq. 1})$$

Percentage elongation

When stress is applied, a film sample stretches, and this stress is referred to as strain. Strain is basically the deformation of the film divided by the original dimension of the sample. As the plasticizer content increases, the elongation of film is observed.

$$\text{Percentage elongation} = \frac{\text{Increase in length of strip}}{\text{Initial length of strip}} \times 100 \quad (\text{Eq. 2})$$

Folding endurance

Folding endurance is determined by repeated folding of the film at the same place until the film breaks. The number of times the film is folded without breaking is calculated as the folding endurance value.

RESULTS AND DISCUSSION

The λ_{max} of ATMX in phosphate buffer pH 6.8 was found to be 269 nm. FT-IR spectra are shown in figure 3 and 4. By this it was confirmed that drug and excipient are compatible. The thickness was found to be high in films prepared with higher concentration of HPMC 5 cps. The thickness and weight of each formulation was found uniform as it was confirmed by lesser SD values. Surface pH of all the four formulations was near / equal to saliva pH. Drug content was found to be uniform in all formulations developed indicating that the drug is distributed throughout the film uniformly. All the above physicochemical parameters are shown in Table 2.

The results of the mechanical properties and *in vitro* dispersion time of the film are shown in Table 3. The Folding endurance of the patches, with different formulations, was found to be in the range of 26 to 71. All the formulations were flexible. F1 showed excellent results in its dispersion time compared to all but it lacks behind in its mechanical properties. F2 was selected based on

its results on performed evaluation which were all optimum and also had good mechanical properties. F3 and F4 showed very good results in mechanical properties evaluation but their *in vitro* dispersion time is more compared to F2 and also their thickness was increased respectively due to rise in polymer concentration.

Table 2: Physicochemical parameters of prepared oral films

Parameters	Formulation code			
	F1	F2	F3	F4
Weight (mg)	35.1 ± 2.5	48.2 ± 3.5	63.5 ± 2.8	75.5 ± 5.6
Thickness (mm)	0.02 ± 0.01	0.04 ± 0.005	0.06 ± 0.01	0.07 ± 0.005
Surface pH	6.4 ± 0.1	6.5 ± 0.05	6.8 ± 0.03	6.8 ± 0.05
Drug content (%)	99.3 ± 1.2	98.6 ± 0.8	99.1 ± 0.5	99.3 ± 1.4

The values are expressed as mean ± SD

Table 3: Mechanical properties and *in vitro* dispersion time of prepared oral films

Parameters	Formulation code			
	F1	F2	F3	F4
<i>In vitro</i> dispersion time (sec)	10.1 ± 3.5	37.6 ± 3.3	45.7 ± 4.6	50.3 ± 6.1
Tensile strength (gm/mm ²)	7.5 ± 0.86	10 ± 1.35	18.9 ± 1.82	17.4 ± 1.03
% elongation	10.5 ± 4.2	11.3 ± 4.6	12.4 ± 3.5	15.2 ± 5.5
Folding endurance	26 ± 4	65 ± 6	71 ± 5	62 ± 6

The values are expressed as mean ± SD

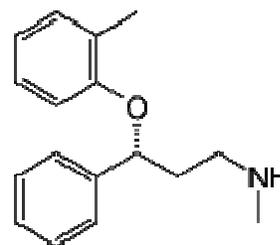


Figure 1: Structural formula of Atomoxetine HCL

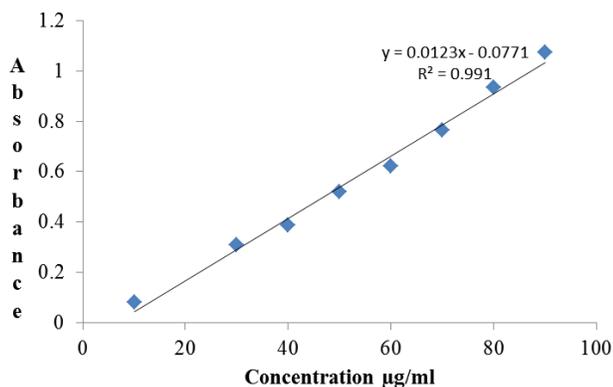


Figure 2: Standard graph of Atomoxetine HCL

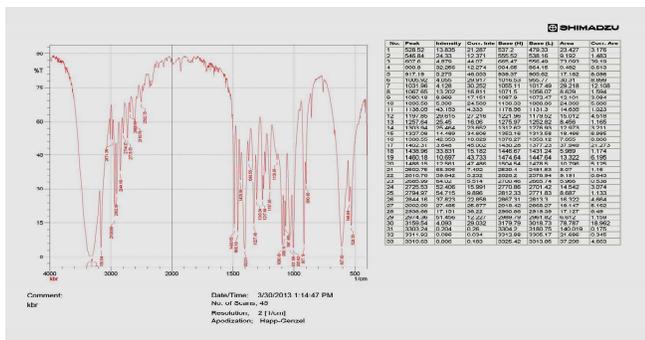


Figure 3: FT-IR Spectrum of Atomoxetine HCL

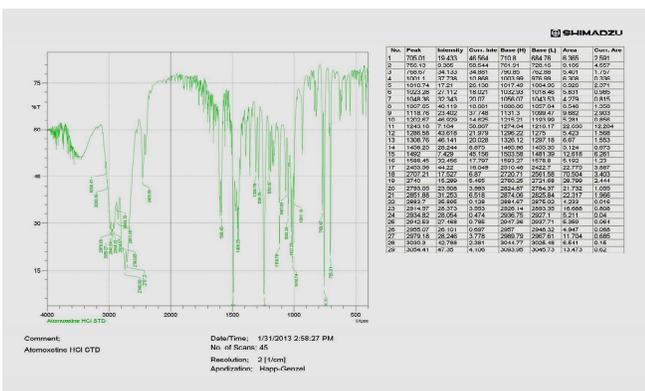


Figure 4: FT-IR Spectrum of mixture HPMC, Atomoxetine HCL



Figure 5: Testing of mechanical property (tensile strength)

CONCLUSION

Mouth dissolving film of atomoxetine HCl was formulated satisfactorily. It showed a good *in vitro* dispersion time along with elegant appearance and other physical characteristics like tensile strength, % elongation, folding endurance. F2 was selected based on its results on performed evaluation which were all optimum and also had good mechanical properties. Therefore it can be a good alternative to conventional Atomoxetine HCl tablets or capsules.

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