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Research Article

FORMULATION AND EVALUATION OF ORAL FILMS OF ATOMOXETINE HYDROCHLORIDE

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ABSTRACT

The objective of the present study was to develop fast releasing oral films of atomoxetine hydrochloride. Good mechanical properties, instant disintegration and an acceptable taste in the oral cavity are the desirable characters that was to be attained. Different groups of films with drug were prepared using different amalgamations of polymers such as HPMC LV grades, sodium alginate, guar gum, PVA and superdisintegrants like SSG, CCS, CP and KYRON 314. The formulations from preliminary trials were optimized using Taguchi OA experimental design. Evaluation test such as weight variation, content uniformity, drug content, folding endurance, thickness, in-vitro dissolution and in-vitro disintegration were done. The optimized films F1 (HPMC LV 50), F4 (HPMC LV 15+ Sodium alginate) and F7 (HPMC LV 15) has disintegration time of less than 30s, releasing 95-100% within 5 min. With a variation in the type of the polymer and concentration of the polymer percentage release and disintegration time varied. Stability studies were conducted for optimized formulations and found to be stable for 1 month.

Keywords: Atomoxetine hydrochloride, Oral Films, HPMC LV Grade, Superdisintegrants, Taguchi OA Experimental Design.

INTRODUCTION

Fast-dissolving drug-delivery systems were formulated as an alternative to tablets, capsules and syrups for paediatric and geriatric patients who experience problems in swallowing conventional oral solid-dosage forms. Henceforth, researchers have developed oral drug delivery that has led to evolution of dosage forms from modest conventional tablets or capsules to improved release tablets or capsules and then to oral disintegrating tablet (ODT) to the recent development of oral fast dissolving films (OFDFs). Patient compliance is an important aspect while considering a formulation of novel drug delivery system (NDDS) [1].

Transdermal patch of fast dissolving films (FDF) are oral drug delivery systems. This thin film is simply placed on the patient's tongue or mucosal tissue, instantly gets wet by saliva, and dissolves rapidly. The medication is released faster due to oral mucosal absorption [2]. Compared to ODTs, ODFs can be prepared using simple preparation process and are easy to carry, store and handle [3]. The novel drug delivery system also be beneficial in the industry for improving the solubility, stability and biological half-life of the drugs [4]. The robustness of the strip depends on the type of polymer used in the formulation [5].

Atomoxetine HCl is the first non-stimulant drug approved for treatment of attention-deficit hyperactivity disorder (ADHD) and is classified as selective norepinephrine reuptake inhibitor with 63% of oral absolute bioavailability in extensive metabolizers due to first pass metabolism by Cytochrome P450 2D6 (CYP2D6) enzymatic pathway. The objective of the work is to prepare fast dissolving films of atomoxetine hydrochloride using various polymers. Optimisation of formulations were done using Taguchi orthogonal array design to minimise the number of formulations.

MATERIALS AND METHODS

Atomoxetine hydrochloride was obtained as gift sample from Mann Medix Pharma ltd, HPMC LV from Kalpana Polymers pvt Ltd, and HPMC LV 50 and guar gum was obtained as a gift sample from Yarrow chemicals Ltd, PVA was obtained from Merck Chemicals Ltd., Mumbai.

Dose calculations of the drug

Diameter of the plate = 6 cm
Radius of the plate = 3 cm
Area of the plate = 28.26 cm^2
Number of 2cm^2 film that can be formed from the whole plate = 28.26/4 = 7.06
Each film contains 2 mg of the drug
7 films contain 14.1 mg of drug
The amount of drug added in each Teflon plate was approximately equal to 14mg.

Solvent casting method is used for this formulation. Excipients used were sodium alginate, poly vinyl alcohol (PVA), guar gum, HPMC LV 15, HPMC LV 50, sodium starch glycolate, cross povidone, croscarmellose sodium, KYRON 314 were used. Before preliminary trails, the films were prepared without superdisintegrants, the film was good, but disintegration was above 2-3 minutes. So, because of this super disintegrates were incorporated in the preparation of oral film. The placebo film was prepared by dissolving the polymer and superdisintegrant, with required quantity of plasticizer (glycerine) and water was added up to 10ml. Then solution was poured into a Teflon plate and was kept at 60º for 24hrs for drying. The best formulations were selected from preliminary trials based on disintegration time. The formulation of oral thin film was shown in table 1[6].

Optimization using Taguchi OA L8 design experiment

Optimization was done using Taguchi OA experiment design. The software used was Minitab-17 English. Independent factors which are type of polymer, % of polymer, type of superdisintegrants, quantity of superdisintigrants studied at 3 levels. Dependent variable (response) was selected as disintegration time. Optimized formulations of the orthogonal array were summarized in table no .2. Experimental designs were summarized in table 3. The optimized formulations were then evaluated for various parameters[6,7].

Physicochemical evaluations of oral films

Films were evaluated for their visual inspection or film formation, weight variation, folding endurance, Drug content, thickness test, In vitro disintegrating test, In vitro dissolution.

Visual inspection and appearance [8]

The films were evaluated visually for its clarity, transparency and stickiness. Films that were satisfactory were evaluated further and if they were unsatisfactory they were discarded.

Weight variation [9]

The test ensures the uniformity of the formed film. From the whole film three small pieces, each of 2×2 cm^2 area and were weighed individually. The standard deviation from the mean value was reported

Folding endurance [10]

Folding endurance was determined by repeatedly folding a small strip of the film at the same place until it breaks. The number of times the film is folded at specific place without breaking gives the folding endurance.

Thickness of film [10]

Appearances of the films were checked for uniformity and for the presence of air bubbles. Thickness of the randomly selected films was determined using Vernier callipers from every batch and the average values were determined.

In vitro disintegration time [11]

Films were placed in a petri plate containing 10 ml of water to determine the in vitro disintegration time. Time taken by the film to get dissolved completely was noted.

In vitro dissolution time [12]

0.1N HCL was used as the dissolution medium to determine the in vitro dissolution study. Forceps was used to place the film in the basket containing 0.1N HCL and the temperature was maintained at 37±0.5°C with a stirring rate of 100 rpm.

Samples were withdrawn at 0, 1, 3, 5, 10 intervals and then replaced by equal volumes of medium. The withdrawn samples are filtered by using what's man filter paper, analysed by UV-Visible spectrophotometer

Drug content [13]

Formulation equivalent to 10 mg of drug was diluted with distilled water and after suitable dilutions the absorbance was measured at 273 nm using UV visible spectrophotometer. The drug concentration was calculated by using the formula.

$$\% \text{ drug content } = \frac{Concentration\ of\ drug\ in\ the\ sample\ solution}{Equivalent\ concentration\ of\ drug\ taken} \text{ x } 100$$

Stability studies

Stability studies were carried out by keeping the optimized formulations in the butter paper followed by aluminium foil and placed in the aluminium pouch, which was heat sealed at the end for one month at room temperature. The films were taken at different time intervals like 0 (initial), 4th week and was analysed for appearance, disintegration time and drug content [6,14]. Results of evaluation parameters for the Taguchi experimental batches given in table 4.

RESULTS AND DISCUSSION

FTIR studies

IR spectra of pure drug atomoxetine HCl showed characteristic absorbance peak at 3442, 2954, 3608, 1242, 1010, 771 indicating Ar-H Stretching, C-H stretching, C-N stretching, Ar-O-R stretching, R-NH stretching, C-O stretching. The peaks identified in the pure drug were relatively same when compared to the polymer blend, resulting no drug polymer interaction that is pure drug is compatible with polymers

Visual inspection

Results of physical appearance of oral film formulations were described in Table 4**.** All the formulations formed a good film which is visually transparent, smooth and thin. Some of the polymers are used alone and some of them are used in combinations showed good film forming capacity and have smooth and transparent appearance. The combination of films such as HPMCLV15+Sodiumalginate and HPMCLV50+Sodium alginate. The combination of natural and synthetic polymers which are used alone or in combinations showed good film forming nature and have smooth and transparent appearance. The films which are formed with good appearance and smooth are used for further evaluations.

Folding endurance

Brittle film has less value of folding endurance and good flexibility gives high value of folding endurance. Optimized films didn't show any cracks even after folding for 100 folds. This can be because as the polymer concentration increases folding endurance value decreases. Optimized formulation revealed to have good film properties [15]. F5 has showed the folding endurance value above 150 [18].

Weight variation

The films have shown a percent weight variation of less than 5%. The variation can be due to the unequal flat surface of the Teflon plates or due to the slant surface of trays in the hot air oven kept for drying. This is an important parameter as difference in weight variation can lead to under or over medication. From, the results it can be concluded that with the increase in the polymer concentration the weight of the film increases.

Table 1: Formulation of oral film

Ingredients	Quantity
Atomoxetine hydrochloride (mg)	14
Polymers (%)	1 & 2
Glycerin (10% w/w of polymer) (mg)	10
Superdisintegrants (mg)	10
Water (QS) (ml)	10

Note: 20 mg aspartame were added to all the formulations

Table 2: Taguchi L8 orthogonal array (4^3) design of experiment

Independent variables	Level 1	Level 2	Level 3
Factor A	HPMC LV 50	HPMCLV15+SA	HPMC LV 15
Factor B	5	10	15
Factor C	Cross povidone	SSG	Kyron314
Factor D	5	10	15

Note: Where, Factor A: Type of polymers, Factor B: % of polymer, Factor C: Type of superdisintegrants, Factor D: Quantity of superdisintegrants

Table 3: Taguchi L^8 experimental runs formulae

Material %(w/v)	F1	F2	F3	F4	F5	F6	F7	F8
HPMC LV 50 (%)	2	3	_	_	_	_	_	_
HPMC LV 15 (%)	_	_	0.5	1	1.5	1	2	3
SA (%)	_	_	0.5	1	1.5	_	_	_
SSG (%)	10	_	15	_	_	_	_	5
CP (%)	_	_	_	_	10	_	15	_
KYRON-314 (%)	_	15	_	_	_	10	_	_

Note- Water: Q.S; F3, F4, F5 are combinations
Atomoxetine HCl: 14mg; 10mg glycerine (10%w/w of polymer); 20mg aspartame were added to all formulation

Table 4: Results of evaluation parameters for the Taguchi experimental batches

FC	Visual inspection	Folding endurance (no. of folds)	Weight variation (mg)	Thickness of film (mm)	Drug content (%)	Disintegration time (sec)
F1	Transparent	138	2.4±0.5	0.21±0.2	96.0±0.23	22.2±0.36
F2	Transparent	150	2.6±0.72	0.24±0.3	95.8±0.28	65.6±0.98
F3	Transparent	110	2.2±0.41	0.26±0.2	98.1±1.21	23.4±0.51
F4	Transparent	141	2.4±0.66	0.31±0.5	99.2±0.21	25.3±0.82
F5	Transparent	165	3.2±0.23	0.30±0.3	98.0±0.25	62.3±1.92
F6	Transparent	122	1.6±0.30	0.27±0.5	98.0±0.37	29.1±0.42
F7	Transparent	148	2.0±0.12	0.22±0.4	97.2±0.35	24.5±0.67
F 8	Transparent	131	1.9±0.98	0.28±0.2	97.80±0.25	58.6±1.80

FC: Formulation code
Note: All the values are express as mean± SD, n=3

Table 5: ANOVA table for disintegration time vs factors A, B, C & D

Source	Degrees of freedom	Sum of squares	Means of squares	F- value	P- Value
A (Type of superdisintegrant)	2	270.2	135.1	0.09	0.913
B (Quantity of superdisintegrant)	2	384.3	142.2	0.10	0.908
C (Type of polymer)	2	745.67	3728.83	245.86	0.000
D (% of polymer)	2	40.17	20.08	0.01	0.987

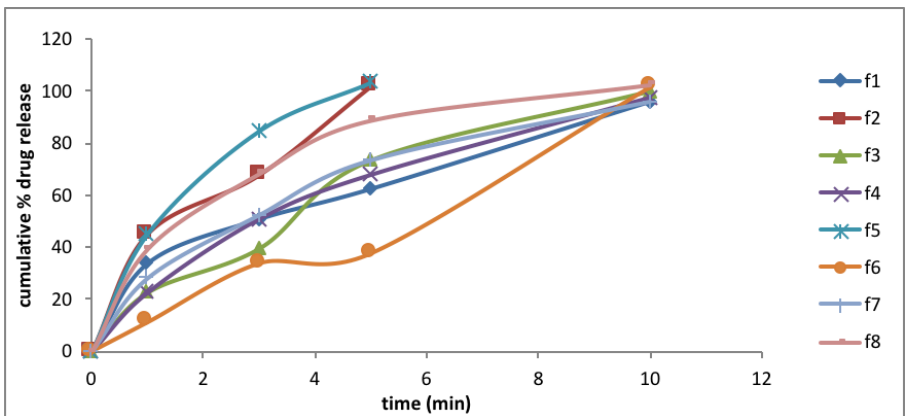

Fig 1: Cumulative percentage drug release of Taguchi experimental batches

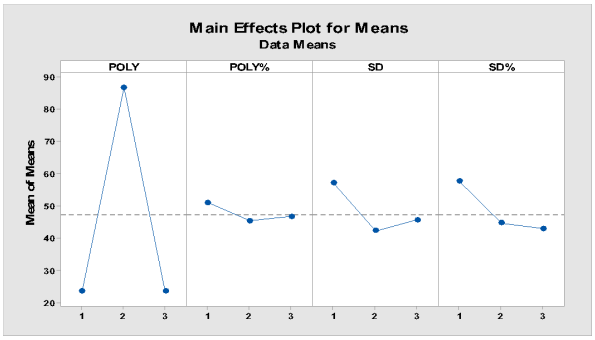

Fig 2: Main effect plots for means

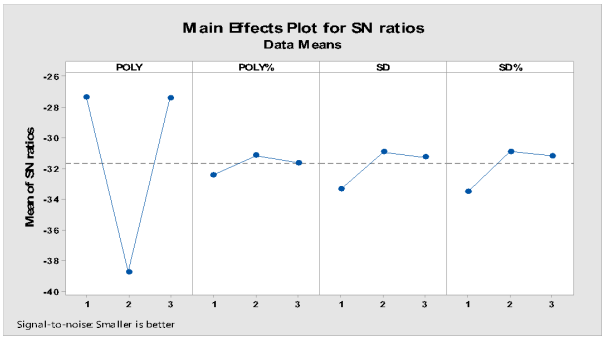

Fig 3: Main effects plot for signal to noise ratios

Thickness of film

The average thickness of the film varied from film to film (30-50 µm). This variation can be attributed to the polymer concentration which is having a direct impact on the thickness[16]. Standard deviation was found to be 0-5%. Lower sensitivity of Vernier callipers (0.01mm) and the surface of Teflon plates not having ideal flat surface or due to slant surface of trays in hot air oven where the plates are kept for drying might be the reason.

Drug content

Percentage drug content of the prepared formulations is summarized in Table 4. The content of the drug ranged from 96% to 99%. All the optimized formulations were found to have drug content within limits which indicates that efficient loading and uniform distribution of drug throughout the film [16].

Disintegration time

Disintegration time plays an important role. It is the time taken by the film to gets dissolved.
There are no official guidelines available for determining disintegration time of orally fast disintegrating films [17]. The normal disintegration time of oral films is ~1 minute[14]. Different combinations were used for the preparation of the films. The disintegration times of all the films were noted and it was found that F1, F4 and F7 showed 22-30sec disintegration time compare to other formulations.

In-vitro dissolution studies

0.1N HCL was used for in-vitro dissolution studies. Prepared films of 2 cm^2 were evaluated. Fig 1. Shows the drug release profile of the optimized formulations. The formulations F2 and F5 exhibited 101.5 and 103.1 % of drug release within 5 minutes. The formulations, F1, F3, F4, F6, F7 and F8 shows percentage drug release of above 95% within 10 minutes. Cumulative percentage drug release of Taguchi experimental batches shown (Fig 1) [19].

Analysis of results using Taguchi design

The obtained results (disintegration time) i.e., response was analysed by Minitab 17 English software. Signal to noise ratio (S/N) for 'lower is the best' characteristic was chosen[2]. From the main effect plot means (fig 2). It can be inferred that factor A (type of polymer) has greatest influence on disintegration time. The other three factors B, C and D (% of polymer, type of superdisintegrant and amount of superdisintegrant) has equal influence on response. The order on which disintegration time (response) depends was type of polymer > type of superdisintegrant > amount of superdisintegrant > % of polymer. One-way ANOVA was used in the analysis of Taguchi design of experiment. Results were summarised in table 5. ANOVA is used to determine whether the factors are significantly related to the response). It was found that type of polymer has significant effect on the disintegration time as the 'P' value is 0.000 at 95% confidence interval ($p<0.05$) [2,20].

CONCLUSION

Atomoxetine HCl was successfully formulated as oral thin film. Drug excipient compatibility concluded that the drug and excipient were compatible with each other. Taguchi L8 orthogonal array (4^3) design experiment was used to study the effect of polymers, % of polymer, type of superdisintegrant and quantity of superdisintegrant at 4 different levels. Optimized formulations were evaluated for physicochemical evaluation. Statistical analysis of Taguchi results suggests that factor A i.e. concentration of polymer has pronounced and significant effect on the response i.e., disintegration time, while factor B, C and D i.e. % of polymer, superdisintegrant, and quantity of superdisintegrant has no pronounced or significant effect on the response. The optimised formulations were found to be stable for one month at room temperature.

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