FAST DISSOLVING TABLETS OF PIMOZIDE: DESIGN, OPTIMIZATION AND *IN VITRO* CHARACTERIZATION

Raja Rajeswari Kamiseti^{1*}, Moses Mekala², Sudhakar Muvvala²,
Durga Bhavani Penmatsa¹

¹Vishnu Institute of Pharmaceutical Education and Research, (Affiliated to Jawaharlal Nehru Tech. University, Hyderabad), Narsapur, Medak, Hyderabad 502 313.

²Malla Reddy College of Pharmacy (Affiliated to Osmania University), Dhulapally, Maisammaguda, Secunderabad. 500 014.

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*Corresponding author
Raja Rajeswari Kamiseti

Email:
rajeswarimpharm@gmail.com

ABSTRACT

As precision of dosing and patient compliance become an important prerequisite for a long-term treatment of Tourette's syndrome there is a need to develop formulation for this drug, which overcomes problems such as difficulty in swallowing, inconvenience in administration while travelling and patient's acceptability. The present work was undertaken with a view to develop a fast dissolving tablets of Pimozide using Kyron T-314 as super-disintegrant along with Avicel PH 102 as diluent by response surface method using direct compression. Drug-excipient compatibility studies were confirmed by FTIR Spectroscopy. The tablets were evaluated for hardness, friability, weight variation, wetting time, disintegration time and uniformity of content and *in vitro* dissolution. Based on evaluating parameters, formulation prepared by using 4.5% Kyron T-314 with 11.5% Avicel PH-102 was selected as optimized formulation and Formulation (F3) had disintegration time of 7.63 ± 0.25 s and percentage cumulative drug release of 81.60 after 10min. The formulations were further studied and confirmed for their stability. Hence it was concluded that direct compression using Kyron T-314 superdisintegrant and Avicel PH 102 was simple and economic technique which can be used for formulation of fast dissolving tablets of Pimozide.

Key word: Pimozide, Tourette's syndrome, fast dissolving tablets, Kyron T 314, direct compression

INTRODUCTION

Across a wide variety of disease states, recent advances in drug delivery technologies have led to the development of innovative delivery systems designed to improve therapeutic outcome. Emerging delivery platforms for improved convenience and adherence with psychiatric medications is achieved with fast dissolving tablets (FDTs) which are ahead among the novel oral drug-delivery systems especially in pediatric and geriatric population with Dysphagia (Kane *et al.*, 2003).

Tourette's syndrome is a chronic neuro developmental disorder characterized by repetitive, stereotyped, involuntary movements and vocalizations called tics which have a significant impact on patients' daily functioning across many domains. Tics tend to be most severe in child and adolescent sufferers, so their presence has the potential to impact a period of life that is both critical for learning and is often associated with the experience of greater social

tension and self-consciousness than adulthood. Furthermore, control over tics that lead to physical impairment or self-injurious behavior is vital importance in maintaining of health and quality of life (James *et al.*, 2002).

Pimozide is an orally active antipsychotic agent of the diphenyl-butylpiperidine series indicated for the suppression of motor and phonic tics in patients with Tourette's syndrome who have failed to respond satisfactorily to the standard treatment (Clare *et al.*, 2011). Pimozide also has less potential for inducing sedation and hypotension as it has more strong and specific dopamine receptor blocking activity upon the post synaptic dopamine receptor than other neuroleptic agents and therefore a suitable alternative to haloperidol (Seemen 2002). Pimozide has an elimination half-life of 55h and undergoes hepatic metabolism and has about 40-50% bio-availability (Fog, 1980; Logan *et al.*, 1982).

Table I. Level of formulation variables

	Name	Units	Low	High	-alpha	+alpha
A [Numeric]	Kyron T-314	mg	9	15	7.75736	16.2426
B [Numeric]	Avicel PH 102	mg	12	23	9.72183	25.2782

Table II. Formulation of FDTs of pimoziide

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Pimozide	1	1	1	1	1	1	1	1	1
Kyron T-314	9	9	9	12	12	12	15	15	15
Avicel PH 102	12	17	23	12	17	23	12	17	23
Mannitol	171	166	160	168	163	157	165	160	154
Acryflow-L	3	3	3	3	3	3	3	3	3
Talc	4	4	4	4	4	4	4	4	4
Total weight	200	200	200	200	200	200	200	200	200

1 and 3 shows *CSF3_{syn}.Ec3* as restriction product D. Colony PCR of BL21(DE3)_pET32a(+)_*CSF3_{syn}.Ec3* with R- and F- insert gene primers. M = 1 kb DNA Marker; NC = negative control; PC = positive control or recombinant plasmid pET32a(+)_*CSF3_{syn}.Ec3*

The solubility of pimoziide in water is less than 0.01mg/mL; slightly soluble in most organic solvents.

Fast dissolving tablets combines the advantages of both liquid and conventional tablet formulations, while also offering advantages over both traditional dosage forms like enhanced bioavailability, avoidance of first pass hepatic metabolism and convenience. Various techniques used in formulating FDTs include Molding Moulding (Habib *et al.*, 2000), Spray drying (Biradar *et al.*, 2006) Mass extrusion, Sublimation, Direct compression, Freeze drying /lyophilization, Cotton candy process (Reddy *et al.*, 2002., Khalid *et al.*, 2011), Phase transition techniques (Sadhana *et al.*, 2013) etc. Direct compression technique (Dobetti *et al.*, 2001) utilizes conventional equipment, commonly available excipients and a limited number of processing steps makes this the easiest process to manufacture FDTs. High doses can be accommodated and the final weight of the tablet can easily exceed that of other production methods. Kyron T-314 is a novel polacrillin potassium superdisintegrants derived from cross linked polymer of Polycarboxylic acids as per USP/NF & has the K⁺ ionic form. It is a very high purity polymer used in pharmaceutical formulations as a super-fast disintegrants as well as dissolution improver in solid dosage forms like tablets, capsules, pellets etc

(Chaudary *et al.*, 2005). Acry flow-L is chemically poly 12-hydroxy stearate widely used in oral dosage formulations as an excellent tablet lubricant. It is high molecular weight polymer and does not get absorbed by body tissue and hence safe for human consumption and hence has no physiological action at recommended dosage (Bi *et al.*, 1995).

An attempt has been made to develop fast dissolving tablets of pimoziide with a novel superdisintegrant Kyron T-314 using response surface method by direct compression method. Based on the preliminary studies, the ranges for the formulations were selected, the response (dependent) variables being Disintegration time (DT).

MATERIAL AND METHODS

Pimozide was gifted by Vasudha Pharma Chem Pvt Ltd, Hyderabad. Kyron T314 and Acry flow L were obtained as gift samples from Corel Pharma Chem., (Ahmedabad, India). All other chemicals and reagents used were of analytical grade and used as supplied by the manufacturer.

Experimental design

Solubility study of pimoziide

Solubility studies of pimoziide were carried out in 0.01N HCl, acetate buffer pH 4.5, phosphate buffer pH 6.8, phosphate buffer pH 7.2 and distilled water.

A sample of 20mg of pure pimozide was taken in 15mL screw cap test tubes containing 10mL of media. The solutions were shaken and kept aside for 24h with continuous stirring. After 24h, the sample solutions were filtered through Whatmann filter paper which a filtrate of 1mL was diluted to a suitable concentration with respective buffer media. The absorbance of the prepared dilutions were measured at 278nm using UV-Visible spectrophotometer. The results were tabulated as shown in table III

Experimental design

The present study involved Response Surface Method with 2 factors as shown in table I. Experimental trials were performed as shown in table II.

Formulation of fast dissolving tablets

FDTs were prepared by direct compression method. Nine different formulations were prepared using Kyrone T 314 as a superdisintegrants and Avicel PH 102 as diluent. All the ingredients (Pimozide, mannitol, Avicel pH 102), except Acry flow L and Talc were passed through 60 mesh size separately and mixed. Then Acry flow L and Talc as Lubricant and Glidant respectively were added and compressed into tablet using 8mm punch on rotary tablet compression machine. Table II show the formulation of FDTs of Pimozide.

Evaluation of FDTs

The FDTs were studied further for chemical interaction using Infra-red Spectroscopy. The results were shown in figures 1 and 2 and table IV.

Evaluation of pre-compression parameters

The prepared powder tablet blend was evaluated for their pre-compression parameters including bulk density (D_b), tapped density (ρ_t), Carr's compressibility index (I), Hausner ratio (H) and Angle of Repose (θ). The results were shown in table V.

Evaluation of post-compression parameters

FDTs were evaluated for post-compression parameters like weight variation, Hardness, Friability, and thickness. The results were tabulated as shown in table VI.

Wetting time and water absorption ratio

Wetting time and water absorption ratio were calculated by taking a piece of tissue paper of internal diameter 6.5cm was folded twice and placed in a small petri dish containing 6mL of water. A tablet was put on the middle of the paper, and the time for complete wetting was measured. The wetted tablet was reweighed to calculate the water absorption ratio was calculated by the following formula: $R = 100 \times (W_a - W_b) / W_a$

Where W_a is weight of tablet after water absorption and W_b is weight of tablet before water absorption. Three trials for each batch were performed and standard deviation was also determined.

In vitro dispersion time

The study was conducted by placing a tablet in a beaker containing 10mL of pH 6.8 buffer at $37 \pm 0.5^\circ$ and the time required for complete dispersion was determined.

Drug content uniformity

The content uniformity was determined by Placing a tablet in a 50mL round-bottomed flask (RBF), add 5mL of 0.1N HCl, and shaken by mechanical stirrer for 30min to which 20mL of methanol was added and shaken for 20 more minutes. Dilutions with methanol were made to obtain a solution having a concentration of about $40 \mu\text{g}$ of Pimozide per mL, mixed centrifuged at 1000rpm. Concomitantly, the absorbance of the solution of Pimozide was observed at 277nm, using a double beam UV-Visible spectrophotometer (TDT-08L, Electrolab, India), against methanol as a blank. Further the drug content was measured using the formula as below: $(TC/D) (A_U/A_S)$

Where 'T' is the labeled quantity of Pimozide (in mg) in the Tablet, 'C' is the concentration, in μg per mL, of Pimozide in the Standard solution, 'D' is the concentration, in $\mu\text{g}/\text{mL}$, of Pimozide in the solution from the tablet.

' A_U ' and ' A_S ' are the absorbance of the solution from the tablet and the Standard solutions respectively.

Table III. Solubility behavior of pimozone

Buffers	Absorbance	Concentration (mg/mL)
0.01 N HCl	0.255	0.023091
4.5 pH	0.241	0.021818
6.8 pH	0.196	0.017727
7.2 pH	0.130	0.011727
H ₂ O	0.079	0.007118

Figure 1. IR Spectra of pimozone.

Figure 2. IR Spectra of pimozone and physical mixture with excipients.

***In vitro* disintegration time**

In vitro disintegration test was carried out in USP tablet disintegration apparatus by placing one tablet in each of the 6 tubes of the basket containing pH 6.8 phosphate buffer as medium maintained at $37 \pm 2^\circ\text{C}$. The time required in seconds for the complete disintegration of the tablet with no visible mass remaining in the apparatus was measured and recorded. The results of wetting time, *in vitro* dispersion time, drug content uniformity and *in vitro* disintegration time were shown in table VII.

***In vitro* dissolution studies**

In vitro dissolution studies were carried out in USP Type II paddle apparatus (Lab India, India) maintained at $37 \pm 0.5^\circ\text{C}$ using 900mL of phosphate buffer pH 6.8 as the dissolution medium at 50rpm. Aliquots of the samples were collected at specified time intervals and were replaced with the fresh medium after each withdrawal. The samples were observed for their respective absorbances at 277nm by UV spectrometry and their cumulative percentage drug release was calculated (Figure 3 and 4).

Table IV. Drug-excipient interactive studies.

NO	Wave number in formulation (cm ⁻¹)		Characteristic wave number range (cm ⁻¹)	Bond nature and bond attributed
	Pure drug	Optimized formulation		
1	3219.42	3281.91	3400-3250	N-H stretching
2	1697.36	1697.08	1640-1690	C=O stretching(amines)
3	1635.29	1639.31	1550-1640	N-H bending (amines)
4	1507.89	1511.85	1400-1600	C=H stretching in Aromatics.
5	1223.23	1250.52	1000-1400	C-F strong stretching Mono substituted cycloalkane
6	692.11	693.93	690-710	C-H deformation

TableV. Evaluation of pre-compression parameters of fast dissolving tablets

Formulation code	Bulk density (gm/cc)	Tapped density (gm/cc)	Angle of repose (degrees)	Carr's index (%)	Hausner ratio
F1	0.48±0.12	0.58±0.10	27.47±0.11	17.241±0.11	1.208±0.11
F2	0.47±0.10	0.57±0.10	24.70±0.11	17.544±0.12	1.213±0.12
F3	0.46±0.13	0.57±0.10	26.59±0.10	19.298±0.10	1.239±0.10
F4	0.49±0.11	0.59±0.11	26.54±0.13	16.949±0.14	1.204±0.13
F5	0.47±0.11	0.6±0.10	25.64±0.11	21.667±0.10	1.277±0.10
F6	0.47±0.11	0.59±0.12	25.41±0.13	20.339±0.1	1.255±0.22
F7	0.45±0.13	0.57±0.14	24.70±0.10	21.053±0.11	1.267±0.11
F8	0.47±0.11	0.59±0.13	25.61±0.10	20.339±0.12	1.255±0.11
F9	0.46±0.11	0.56±0.11	23.79±0.12	17.857±0.11	1.217±0.13

Table VI. Evaluation of post-compression parameters of fast dissolving tablets

Formulation code	Hardness + SD (kg/cm ²)	Friability (%)	Thickness (mm)	Weight variation + SD (mg)
F1	3.05±0.53	0.55±0.15	2.97±0.058	197.43±2.23
F2	3.12±0.121	0.56±0.11	2.92±0.053	199.14±2.91
F3	3.11±0.102	0.4±0.11	2.93±0.061	197.57±2.3
F4	3.09±0.091	0.51±0.12	2.98±0.075	197.14±2.19
F5	3.15±0.139	0.85±0.11	2.96±0.036	196.71±1.98
F6	3.14±0.131	0.6±0.11	2.87±0.08	197.43±2.15
F7	3.13±1.125	0.66±0.15	2.92±0.045	196.86±2.04
F8	3.12±0.122	0.72±0.11	2.93±0.070	198.57±2.07
F9	3.16±0.077	0.65±0.11	2.90±0.042	198.43±2.76

Stability studies

Short-term stability studies on the promising formulations (F3) were carried out by storing the tablets in an amber coloured rubber stoppered vial at 40°/75% RH for 3 months. At an interval of 1 month, the tablets were visually examined for any physical changes, changes in drug content and *in vitro* dispersion time.

RESULTS AND DISCUSSION

Solubility studies showed distinct solubility of Pimozide very poor solubility in distilled water and moderate solubility in buffers of pH 7.2 and 6.8. The drug was found to have better solubility in 0.01N H Cl and buffer of pH 4.5 (Table III). The results indicate that there were no possible chemical interactions between the drug and the

Table VII. Evaluation of post-compression parameters of fast dissolving tablets

Formulation Code	Wetting time + SD (Sec)	Disintegration time + SD (Sec)	% Drug content
F1	15.5±0.66	8.30±0.19	98.43±0.98
F2	15.4±0.44	9.4±0.26	97.37±1.4
F3	14.5±0.35	7.63±0.25	99.10±1.97
F4	16.8±0.36	8.6±0.30	98.90±1.9
F5	17.3±0.46	10.48±0.3	98.33±2.61
F6	16.6±0.53	9.36±0.25	98.33±2.61
F7	17.3±0.60	9.7±0.26	96.10±1.37
F8	20.9±0.56	10.8±0.53	97.57±1.22
F9	21.2±0.36	10.9±0.20	97.23±1.5

Figure 3. Invitro dissolution profile of FDTs of Pimozide

Figure 4. Contour plot of FDTs of pimozide

excipients (Figure 1, 2 and Table IV). The pre-compression parameters were found to be within the specified limits and shown on Table V. The results of evaluation post-compression parameters were found to be within the limits (Table VI and VII)

In vitro dissolution time profile Optimization

The Model F-value of 16.56 implies the model is significant. There is only a 0.09% chance that an F-value this large could occur due to noise. Values of "Prob> F" less than 0.0500 indicate model terms are significant.

The optimization model was found to be significant with F value 33.32 and p-value of 0.0027. It was found that disintegration time increased with an increase in the concentration of Kyron T 314. Formulation F 3 got disintegrated in 7.63s. Hence it was concluded that Formulation F3 was optimized.

Stability studies

Accelerated stability studies on the promising formulations (F3) were found to have physical stability without any morphological changes and the drug content was found to be within the limits.

CONCLUSION

Hence it has been concluded that Design of Experiments following Response Surface Methodology can be effectively used in the design, formulation and evaluation of FDTs of drugs. By adopting a systematic formulation approach (DOE-RSM), an optimum point can be reached in the shortest time with minimal efforts. Pimozide fast dissolving tablets can be successfully prepared using Kyron T-314 as superdisintegrant which effectively reduces the disintegration time and thus enhance patient compliance.

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