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Research Article

FORMULATION DEVELOPMENT AND EVALUATION OF AMISULPRIDE ONCE DAILY TABLET

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ABSTRACT

The objective of the present study was to develop once-daily tablet of Amisulpride, a second generation antipsychotic, a substituted Benzamide. The tablets were prepared by the wet granulation method. Microcrystalline Cellulose, Hydroxy Propyl methylcellulose (HPMC), Talc, Magnesium Stearate, Iso Propyl alcohol, Xanthan Gum, Kollidone, Cross Pobidone, Aerosil, Avesil 101, 112, 102, Sodium Bi-carbonate, Poly vinylpyrollidone K-30, Carbopol with varying excipients Six bilayer formulations AM_1-AM_6 were prepared by compressing both Instant Release (IR) and Sustained Release (SR) granules. The granules were evaluated for bulk density, tapped density, compressibility, Hausner ratio and moisture content. The tablets AM_1-AM_6 were evaluated. The granules showed satisfactory flow properties. All the tablets formulations showed acceptable Pharmacotechnical properties and complied within specifications for tested parameters. The results of dissolution studies indicated that the formulation AM_1, AM_2 and AM_3 the release retardant use in combination of SR part & IR part, AM_1(80:20), AM_2(80:20)in combination of HPMC and poloxmer 188 and AM_3 use is xanthane gum but process not fissile and dissolution was faster. Formulation AM_6 exhibited satisfactory drug release; amisulpride OD Bi-layer 400 mg tablets dissolved more than 90% in 24 hours.

KEYWORDS: Amisulpride, Sustained release, once daily tablet

INTRODUCTION

Schizophrenia is the most common form of severe mental illness, with a lifetime risk of developing the disease of about 1%[1].There is no 'cure' available for schizophrenia. Traditional or 'typical' antipsychotic drugs (neuroleptics), such as chlorpromazine and haloperidol, appear to act centrally by blocking dopamine (D_2) receptors in the brain. As a group, they relieve symptoms in at least 75% of patients during an acute attack[2].Amisulpride is another atypical antipsychotic agent, structurally similar to sulpiride. It differs from other atypical in that it exhibits selective affinity for dopamine D_2 and D_3 receptors only. The effectiveness of amisulpride in improving both the positive and negative symptoms of schizophrenia probably relates to its different effects on dopaminergic transmission at high and low doses[3,4]. To characterize the role of the 5-HT_7 receptor in the antidepressant effects of amisulpride, a study prepared 5-HT_7 receptor knockout mice. These results indicate that 5-HT_7 receptor antagonism plays a major role in the antidepressant effects of amisulpride[5]. Amisulpride and its relative sulpiride have been shown to bind to and activate the GHB receptor at doses that are used for therapeutic purposes[6].Amisulpride 400-1200mg/day was found to be as least as effective. At low doses amisulpride demonstrated a similar safety profile to placebo. At higher doses adverse events such as endocrine effects, agitation, insomnia and anxiety occurred at a similar rate to that seen with other antipsychotics. It has no

affinity for serotonergic alpha-adrenergic, H_1 histaminergic or cholinergic receptors. Amisulpride acts preferentially on presynaptic receptors increasing dopaminergic transmission at low doses[7]. There are two absorption peaks - one hour post-dose and a second 3-4 hours after taking the tablet. The elimination half-life is 12 hours. Absolute bioavailability is 48%.Amisulpride is weakly metabolized by the liver. There are two inactive metabolites. The drug is mainly eliminated unchanged by the kidney. 50% of an IV dose is eliminated by the kidney of which 90% is eliminated in the first 24 hours. Drug absorption is rapid, within 3-4 hours of oral administration and to improve patient compliance, a once-daily sustained-release formulation of Amisulpride is desirable. So, amisulpride bi-layer tablets were formulated comprising of IR part and SR part as layers. Because of their flexibility, hydrophilic polymer matrix systems are widely used in oral controlled drug delivery to obtain a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance[8]. Hence, in the present work, hydrophilic matrix materials such as hydroxy propyl methylcellulose are used. Formulations AM_1 to AM_6 are prepared by varying excipients. Microcrystalline Cellulose, Hydroxy Propyl methylcellulose(H.P.M.C), Talc, Magnesium Stearate,Iso Propyl alcohol, Xanthan Gum, Kollidone, Cross Pobidone , Aerosil, Avesil 101,112,102 ,Sodium Bi-carbonate, Poly vinylpyrollidone K-30, Carbopol are used for formulation.

MATERIALS

Amisulpride is purchased from (Anjan drug pvt. Ltd Chennai) Microcrystalline Cellulose (Colorcon India Ltd, Bombay), Ferrous Fed Oxide (Aqualon-USA), H.P.M.C (ISP Technologies, Bombay), Talc and Magnesium Stearate are gifted by (Mittal Polymer, Bombay). Iso Propyl alcohol (M/S National agencies, Bombay), Kollidone (Colorcon labs, Mumbai), Cross Povidone (ROHM Gmbh & co KG-thane Maharastra.), Xanthenes Gum (Ranchem, Avesil 101,112,102 (Ranchem), Sodium Bi-carbonate (Ranbaxy Lab.Ltd.), Poly vinylpyrollidone K-30(ISP Technologies, Bombay), Aerosil, Carbopol were procured from (Degussa).

EVALUATION OF GRANULES

Bulk density

Bulk density is determined by measuring the volume of powder that has been passed through a screen, into a graduated cylinder. A quantity of 100gr of sample from each formula was introduced into a 10ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to tap 500, 750 and 1250 taps and read corresponding values V500, V750 and V1250, to the nearest milli liter. Bulk density was calculated using in the following formula.

$$\textbf{Bulk density} = W/V_o$$

Tapped density

Tapped density is achieved by mechanically tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder is mechanically tapped, and volume readings are taken little further volume change is observed. The tapped density was calculated using in the following formula.

$$\textbf{Tapped density} = W/V_f$$

Compressibility index

The compressibility index of the granules was determined by measuring both the bulk volume and tapped volume of a powder .compressibility index was calculated using in the following formula.

$$\textbf{Compressibility index} = 100XV0\text{-}Vf / V0$$

Hausner ratio

Hausner Ratio was calculated using in the following formula.

$$\textbf{Hausner Ratio} = V0/Vf$$

EVALUATION OF TABLETS

Weight variation test

To study weight variation, 20 tablets for each single dose preparations presented in individual containers were weighed using an electronic balance, and the test was performed according to the official method.

Thickness

The thickness of the tablets was determined using a thickness gauge Five tablets from each batch were used, and average values were calculated.

Drug Content

Five tablets were weighed individually, and the drug was extracted in water. The drug content was determined by weighing, amount of powdered granules (100 mg) was extracted with water and the solution was filtered through 0.45-µ membrane. The absorbance was measured with UV spectrometer after suitable dilution.

Hardness and Friability

For each formulation, the hardness and friability of 6 tablets were determined using the hardness tester and the friabilator, respectively.

In Vitro Release Studies

The in vitro dissolution studies were carried out using USP apparatus type II at 75 rpm. The dissolution medium consisted of 0.1N hydrochloric acid for the first 1 hour , then acetate buffer pH 3.0 to 4 hours and phosphate buffer pH 7.4 from 6 to 24 hours (900 mL), maintained at 37°C ± 0.5°C. The drug release at different time intervals was measured by UV-visible spectrophotometer.

RESULTS

The granules of different formulations were evaluated for LBD, TBD, compressibility index, Hausner ratio and moisture content (**Table 2**). The results of compressibility index (%) ranged from AM_1, AM_2, AM_3, AM_4 and AM_5 are 21.53, 24.71, 20.01, 24.68, 18.46 and 18.40 respectively. The results of bulk density of granules are 0.510, 0.524, 0.560, 0.497, 0.530 and 0.540. And tapped density of the formulations AM_1, AM_2, AM_3, AM_4, AM_5, and AM_6, are 0.650, 0.696, 0.700, 0.661,0.650 and 0.665 respectively. Hausner ratio of the formulations are 1.27, 1.32, 1.25, 1.32, 1.22 and 1.20.The Moisture content of granules of formulations AM_1, AM_2, AM_3, AM_4, AM_5 and AM_6 are 0.81, 0.51, 0.67, 0.52, 0.75 and 0.72% respectively.

The average percentage deviation of 20 tablets of each formula was less than ±5%. Drug content was found to be uniform among different batches of the tablets and ranged from 97.5(3.5) to 101.0(2.5). The hardness and percentage thickness of the tablets of all batches ranged from 140N and 7.10mm respectively (**Table 3**). Friability of the tablets on 100, 200 and 300 RPM are 0.03, 1.04 and 2.03 % respectively. The assay (%) of the formulations ranged from 96.15 to 104.09 and disintegration time of the formulations AM_1, AM_2, AM_3, AM_4 AM_5 and AM_6, are was about 18, 19, 21, 22, 23 and 23 hours ± 45 sec.

The dissolution studies of formulations were subjected to 0.1N hydrochloric acid for the first 1 hour, pH 3.0 acetate buffer for 4 hours and then pH 6.8 phosphate buffer to 24 hours. Results of dissolution studies of the tablets Am_1 released 64.0, 80.0, 88.0 and 103.0 at the end of 4 hours, 8 hours, 12 hours and 24 hours respectively. The release was found to be very fast. In Am_2 the release retardant use is combination of HPMC & Poloxmer 188 and Kollidone SR 100 (80:20) still the dissolution profile is faster In Am_3 the release retardant use is xanthane gum but process not fissile and dissolution still faster (**Table 4**). In Am_4 the release retardant use is water & IPA (70:30) has properties of hydration and erosion produce slow release rate relative to low molecular weight polymer. Fast dissolution profile was achieved, but only 50% release achieved in 6 hrs. Due to fast dissolution profile than required for low viscous grade Carbopol 71G.In Am_5 the release retardant use is HPMC K4M dissolution profile improved but still not achieved for 18hrs and for 6 hrs so next batch planned using NaHCO3 for floating the tablet, so tablet retain in GI fluid by floating & increase the dissolution profile. In Am_6 for floating the tablet we did use the NaHCO3, so tablet retention time increase in GI fluid. Three batches of trial & complied that,

batch 6-A, B&C. results showed that we achieved our objectives that Amisulpride OD Bi-layer 400 mg tablets dissolved more than 90% in 24 hours (**Table 5**). The results of the formulations AM_1-AM_6 are shown in figure

DISCUSSION

Different tablet formulations were prepared by wet granulation technique (**Table 1**). Each tablet contained 400 mg of Amisulpride and other pharmaceutical ingredients as listed in **Table 1**. Prior to the compression, the granules were evaluated for several tests. Bilayer consists of both IR and SR part as layers. SR part of AM_1 was formulated by weighing Amisulpride according loading dose Maintenance dose calculation. Micro Crystalline Cellulose (MCC) Ph 101 & Hydroxy Propyl Methyl Cellulose (HPMC) K4MCR were dispersed & sifted through #24 sieve. HPMC 3 Caps was dispensed & dissolved in 52ml water. Weighed ingredients are loaded in 1 liter RMG Mixed for 10 minute with impeller slow speed & chopper of for 10 min. Mixed material were granulated by HPMC solution with impeller Slow speed &chopper off (Extra water quantity 60ml.), Wet mass was become dough mass. This wet mass was dried. And IR Part is formulated by weighing Amisulpride, Lactose Monohydrate, SSG and Aerosil and co sifted through 20#. Poloxamer 188 was weighed and dissolved in 60.00gm water with stirring HPMC 3Cps was weighed and dispersed into above solution with stirring. This was used as binder. Material was loaded into 1 lit RMG and granulated. The wet mass is dried into rapid dryer at 65 ^oC till L.O.D is within 2 %(L.O.D -1.113%). The dried mass was sized through 1.0 mm screen in oscillating granulator. Sized granules were blended for 10 min. with SSG + Talc +Xyloid passed through 40# in 1 liter blend. Above blend was lubricated with Mg^+ stearate & pass through 60# for 5 min in 1 liter Blend. The formulation AM_3 was modified by taking only placebo, all the excipients except Mg^+ stearate weighed and mixed properly and passed threw 40# sieve. Then the Mg^+ stearate is added to the mixed mass. Now placebo was sent for packing in Alu-Alu blister pouches and kept for stability study.

SR part of AM_2, AM_4, AM_5 and AM_6 are formulated same as AM_1, but using HPMC K4MCR , Kollidone SR, Carbopol 71G, and Sodium bicarbonate and Carbopol 71G respectively. IR part of AM_2 formulated as AM_1 instead of poloxamer 188 poloyoxy & colloidal silicon dioxide was used. IR part of AM_4, AM_5 and AM_6 are formulated same as that of the AM_2. Whereas AM_6 SR part batch of Amisulpride 400mg tablets using $NaHCO_3$ and Carbopol.

CONCLUSION

The release profiles of Amisulpride OD Tablets were compared with our proposed release data. From this study it was concluded that Amisulpride: for floating the tablets we did use the $NaHCO_3$, so tablets retention time increase in GI fluid. So that we get 3 batch of this trial & compiled that batch 6-A, B & C. We have to observe that we achieved our objective that, Amisulpride OD bi-layer 400 mg tablets dissolved more than 90 % in 24 hours by the use of $NaHCO_3$ & above mentioned polymers. With the aim to check the Dissolution of the formulation the Drug formula for Am_6 was charged under 0.1 N Hcl & Phosphate Buffer. The sample for AM_6 achieves the acceptance criteria for Dissolved in 24 hours in dissolution medium.

REFERENCE

1. Schizophrenia: The forgotten Illness. SANE Mental Health Series No.1.
2. Anon. The drug treatment of patients with schizophrenia. *DTB* 1995; 33(11): 81-86.
3. Anon. Solian. Summary of Product Characteristics. Lorex Synthélabo Ltd. August 1997.
4. Coukell AJ, Spencer CM & Benfield P. Amisulpride: A review of its pharmacodynamic and pharmaco-kinetic properties and therapeutic efficacy in the management of schizophrenia. CNS Drugs 1996; 6: 237-256
5. Abbas AI, Hedlund PB, Huang XP, Tran TB, Meltzer HY, Roth BL. Amisulpride is a potent 5-HT (7) antagonist: relevance for antidepressant actions in vivo." Psychopharmacology (Berl) 2009
6. Maitre M, Ratomponirina C, Gobaille S, Hodé Y, Hechler V (Apr 1994). "Displacement of [3H] gamma-hydroxybutyrate binding by benzamide neuroleptics and prochlorperazine but not by other antipsychotics". Eur J Pharmacol. 256 (2): 211–4.

7. Boyer P, Lecrubier Y, Stalla Bourdillon A, Fleurot O. Amisulpride versus amineptine and placebo for the treatment of dysthymia. Neuropsychobiology, 1999; 39:1, 25-32.
8. Lordi GN. Sustained release dosage forms. In: Lachman L, Liberman HA, Kanig JL, eds. The Theory and Practice of Industrial Pharmacy. Mumbai, India: Varghese Publishing House; 1987:430-456.

Table 1: Formulation of the Amisulpride OD Tablets (400mg)
quantities in per Tablets

INGREDIENTS	AM1	AM2	AM3	AM4	AM5	AM6
Amisulpride	400	400	--	400	400	400
Polyvinyl Pyrollidine K-30	8.00	8.00	8.00	8.00	8.00	8.00
IPA	30%	30%	40%	20%	20%	20%
Water	70%	70%	60%	80%	80%	80%
Avesil	10.2	10.2	10.2	15.00	15.00	15.00
Polyox	--	17.90	17.90	--	--	--
HPMC K4M	--	95.00	95.00	100.26	100.26	100.26
Carbopol 71G	--	--	20	20	20	20
Aerosil		64	64	64	64	64
Talc	19.75	19.75	19.75	19.75	19.75	19.75
Cross Carmelose Sodium	5.51	5.51	5.51	5.51	5.51	5.51
Starch	150.00	150.00	150.00	200.00	215.00	200.00
Kollidone SR	--	--	--	21.32	21.52	21.32
NaHCO3	--	--	--	--	--	15.20
Xanthane Gum	3.50	3.50	3.50	--	--	--
Mag. Stearate	1.50	1.50	1.50	4.50	4.50	4.50
Total	**750**	**860.00**	**860.00**	**990.00**	**990.00**	**9.990**

Table 2: Characteristics of granules of Amisulpride OD Tablets formulation

Sr. no	Formulation	Bulk density g/ml	Tapped density g/ml	Compressibility index (%)	Hausner ratio	Moisture content (%)
1	AM1	0.510	0.650	21.53	1.27	0.81
2	AM2	0.524	0.696	24.71	1.32	0.51
3	AM3	0.560	0.700	20.01	1.25	0.37
4	AM4	0.497	0.661	24.68	1.32	0.52
5	AM5	0.530	0.650	18.46	1.22	0.75
6	AM6	0.540	0.665	18.40	1.20	0.72

Table 3: Physico-chemical properties of Amisulpride OD Tablets formulation

S.No	Formulation	Weight variation	Content uniformity	D.T	Assay
1	AM1	750±5%	101(2.5)	18 hour 30 sec	102.1
2	AM2	860±5%	99.84(2.1)	19 hour 30 sec	97.83
3	AM3	860±5%	100.1(2.5)	21 hour 45 sec	96.15
4	AM4	990±5%	97.5(3.5)	22 hour 10 sec	104.09
5	AM5	990±5%	98.99(3.1)	23 hour 20 sec	101.13
6	AM6	990±5%	99.10(2.9)	23 hour 40 sec.	101.11

Table 4: Mean cumulative percentage release of Amisulpride OD Tablets from (Inventive Product) in 0.01 Hcl, pH 7.5 at 50 rpm USP type II apparatus

MEDIUM	TIME (hrs)	(BATCH NO: 400/01) % drug dissolved 75RPM (IR:SR=30:70) HPMC K4MCR	(BATCH NO: 400/02) % drug dissolved 50 RPM (IR:SR=30:70) HPMC K4MCR	(BATCH NO: 400/03) % drug dissolved 75 RPM IR + SR mix (IR:SR=30:70) HPMC K4MCR	(BATCH NO: 400/04) % drug dissolved 50 RPM (IR:SR=30:70) HPMC K100MCR	(BATCH NO: 400/05) % drug dissolved 50 RPM (IR:SR=20:70) HPMC K4MCR	(BATCH NO: 400/06A) % drug dissolved 50 RPM (IR:SR=20:70) HPMC K100MCR
0.1 NHCL	1	44.0	45.0	17.0	45	31	34
pH 3.0 Acetate Buffer	2	53.0	55.0	28.0	54	45	46
	3	59.0	60.0	38.0	59	52	53
	4	64.0	66.0	45.0	61	57	57
pH 6.8 phosphate Buffer	6	73.0	74.0	58.0	70	68	68
	8	80.0	81.0	66.0	75	74	75
	12	88.0	89.0	76.0	83	82	84
	18	98.0	97.0	86.0	89	86	90
	24	103.0	101.0	84.0	93	93	95
Remarks							RSD more

Dissolution data:
Media volume: 900ml
Apparatus: USP II

Table 5: Mean cumulative percentage release of Amisulpride OD Tablets from (Inventive Product) in 0.01 Hcl, pH 7.5 at 50 rpm USP type II apparatus.

MEDIUM	TIME (hrs)	(BATCH NO: 400/6B, % drug dissolved	(BATCH NO: 400/06C, %drug dissolved (50mg extraNaHCO3)
0.1 N HCl	1	32	35
	2	40	44
	3	46	49
	4	51	54
pH 6.8 Phosphate Buffer	6	58	60
	8	65	66
	12	75	75
	18	83	82
	24	89	88

Dissolution data
RPM: 50
Media volume: 900ml
Appratus: USP II

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