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A Review on "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, HydroxyPropylmethyl cellulose (HPMC), Talc, Magnesium Stearate, Iso Propyl alcohol, Xanthan Gum, Kollidone Cross Pobidone, Aerosil, Avesil 101, 112, 102, Sodium B i-car bonate, 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, and 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.

Key Words: Amisulpride, Sustained release, Once daily tablet, Schizophrenia, Acute psychosis, Efficacy, Safety

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) 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_3receptors 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_7receptor in the antidepressant effects of amisulpride, a study Prepared 5-HT_7receptor 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 r ate 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 hour s 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 I R 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 hydroxypropyl methylcellulose are used. Formulations AM_1 to AM_6 are

prepared by varying excipients. Microcrystalline Cellulose, Hydroxypropylmethylcellulose (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) [9].

Release Rate and Dose Consideration

As already mentioned, conventional dosage forms include solutions, Tablets, Tablets, emulsions, etc. These dosage forms can be considered to release their active ingredients into an absorption pool immediately.

$$\text{Dosage form} \xrightarrow{K_r} \text{Absorption pool} \xrightarrow{K_a} \text{Target area} \xrightarrow{K_e}$$

Drug release absorption elimination

The absorption pool represents a solution of the drug at the site of absorption.

Where

K_r= First order rate constant for drug release.

K_a=First order rate constant for drug absorption.

K_e=First order rate constant for overall drug elimination.

For immediate release dosage forms $K_r >>> K_a$ or alternatively absorption of drug across a biological membrane is the rate-limiting step in delivery of the drug to its target area [10].

For non-immediate release dosage forms, $K_r <<< K_a$, that is, release of drug from the dosage form is the rate limiting step. This cause the above kinetics scheme to reduce to

$$\text{Dosage form} \longrightarrow \text{Target area} \longrightarrow$$

Drug release elimination

Potential Advantages of Controlled Drug Therapy: All controlled release products share the common goal of improving drug therapy over that achieved with their non-controlled counter parts. This improvement in drug therapy is represented by several potential advantages of the use of controlled release systems are [11,12]

A) Avoid patient compliance problems.

B) Reduction in total dose administered, thereby,
   i) Minimize or eliminate local side effects.
   ii) Minimize or eliminate systemic side effects.
   iii) Obtain less potentiation or reduction in drug activity with chronic use.
   iv) Minimize drug accumulation with chronic dosing.

C) Improve efficiency in treatment.
   i) Cure or control condition more promptly.
   ii) Improve control of condition i.e. reduce fluctuation in drug level.
   iii) Improve bioavailability of some drugs.
   iv) Make use of special effects e.g. Sustained release aspirin for morning relief of arthritis by dosing before bedtime.

D) Economy.

Drug Properties relevant to sustained release formulation

The design of controlled-release delivery systems is subject to several variables of considerable importance. Among these are the route of drug delivery, the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug. Each of these variables are interrelated and this imposes certain constrains upon choices for the route of delivery, the design of the delivery system and the length of therapy. Properties of drugs are very important for designing a Sustained release dosage form. Mainly physicochemical and biological properties of the drug are most important [13].

1) Physicochemical Properties

a) Aqueous solubility and pKa: -A drug to be absorbed it first must dissolve in the aqueous phase surrounding the site of administration and then partition into the absorbing membrane. Two of the most important physicochemical properties of a drug that influence its absorptive behaviour are its aqueous solubility and if it is a weak acid or base, its pKa. These properties play an influential role in the performance of controlled release systems [14].

The aqueous solubility of a drug influences its dissolution rate, which in turn establishes its concentration in solution and hence the driving force for diffusion across membrane. Dissolution rate is related to aqueous solubility as shown by the Noyes-Whitney equation that, under sink condition is

$$Dc/dt=K_D A C_s$$

Where

Dc/dt = Dissolution rate

K_D = Dissolution rate constant

A = Total surface area of the drug particles.

C_s = Aqueous saturation solubility of the drug.

b) Partition Coefficient:- Between time that a drug is administered and the time it is eliminated from the body, it must diffuse through a variety of biological membranes that act primarily as lipid like barriers [15]. A major criteria in evaluation of the ability of a drug to penetrate these lipid membranes is its apparent oil/water partition coefficient defined as

$$K=C_0/C_w$$

Where

C_0 = Equilibrium concentration of all forms of the drug e.g. ionized and unionized in an organic phase at equilibrium

C_w = Equilibrium concentration of all forms in aqueous phase.

c) Drug stability:-One important factor for oral dosage forms is the loss of drug through acid hydrolysis and/or metabolism in the GI tract. Since a drug in the solid state undergoes degradation at a much slower rate than a drug in suspension or solution. It is possible to improve significantly the relative bioavailability of a drug that is unstable in GI tract by placing it in a slowly available controlled release form. For those drugs that are unstable in the stomach, the most

appropriate controlling unit would be one that releases its content only in the intestine. The reverse in the case for those drugs that are unstable in the environment of the intestine, the most appropriate controlling unit in this case would be one that releases its contents only in the stomach. So, drugs with significant stability problems in any particular area of the GI tract are less suitable for formulation into controlled release systems that deliver their content uniformly over the length of the GI tract. Controlled drug delivery systems may provide benefits for highly unstable drugs because the drug may be protected from enzymatic degradation by incorporation into a polymeric matrix [16].

d) Protein Binding:-There are some drugs which having tendency to bind with plasma proteins (eg. Albumin) and causes retention of the drug in the vascular space. The main force of attraction responsible for binding is van der Waal's forces, hydrogen bonding and electrostatic forces. In general, charged compounds have a greater tendency to bind a protein than uncharged compounds, because of electrostatic effects.

e) Molecular size and diffusivity:-Drugs in many controlled-release systems must diffuse through a rate controlling membrane or matrix. The ability of a drug to diffuse through membranes, it's so called diffusivity (diffusion coefficient), is a function of its molecular size (or molecular weight).

An important influence upon the value of the diffusivity, 'D', in polymers is the molecular size (or molecular weight) of the diffusing species. For most polymers, it is possible to relate log D empirically to some function of molecular size as

$$\text{Log } D = - S_v \log V + K_V = - S_M \log M + K_m$$

Where

V = molecular volume.

M = molecular weight.

S_V, S_M, K_V, K_m = constant.

2) Biological Properties

1) Absorption:-The rate, extent and uniformity of absorption of a drug are important factors when considering formulating into a controlled-release system. Since the rate-limiting step in drug delivery from a controlled-release system is its release from a dosage form, rather than absorption, a rapid rate of absorption of drug relative to its release is essential if the system is to be successfull [17]. In case of controlled release dosage form $K_r <<< K_a$. This becomes most critical in the case of oral administration. Assuming that the transit time of a drug through the absorption area of the GI tract is between 9 and 12 hrs, the maximum absorption half-life should be 3 to 4 hrs. This corresponds to a minimum absorption rate constant K_a of 0.17 to 0.23 hr^{-1} necessary for about 80 to 95 % absorption over a 9 to 12 hr transit time.

For a drug with a very rapid rate of absorption (i.e. $K_a >>$ 0.23 hr^{-1}), the above discussion implies that a first order release rate constant $K_r <$ 0.17 hr^{-1} is likely to result in unacceptably poor bioavailability in many patients. Therefore, slowly absorbed drugs will be difficult to formulate into controlled release systems where the criterion that $K_r <<< K_a$ must be met.

2) Distribution: -The distribution of a drug into vascular and extra vascular spaces in the body is an important factor in its overall elimination kinetics. Two parameters that are used to describe the distribution characteristics of a drug are its apparent volume of distribution and the ratio of drug concentration in the tissue to that in plasma at the steady state, the so-called T/P ratio. The magnitude of the apparent volume of distribution can be used as a guide for additional studies and as a predictor for a drug-dosing regimen and hence the need to employ a controlled –release system.

3) Metabolism: -Drugs that are significantly metabolized before absorption, either in the lumen or tissue of the intestine, can show decreased bioavailability from slower releasing dosage forms. Most intestinal wall enzyme systems are saturable. As the drug is released at a slower rate to these regions, less total drug is presented to the enzymatic process during a specific period allowing more complete conversion of drug to its metabolite. Formulation of these enzymatic ally susceptible compounds as prodrug is another viable solution [18].

4) Biological Half Life: -The half-life of Amisulpride is 48%.The usual goal of an oral Sustained release product is to maintain therapeutic blood levels over an Sustained period. To this, drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half-life. Each drug has its own characteristic elimination rate, which is the sum of all elimination processes including metabolism, urinary excretion and all other processes that permanently remove drug from blood stream.

Therapeutic compounds with short half-life are excellent candidates for Extended-release preparations, since this can reduce dosage frequency. However, this is limited, in that drugs with very short biological half-life as it may require excessively large amounts of drug in each dosage unit to maintain Sustained effect, forcing the dosage form itself to become large.

In general, drugs with half-life shorter than two hrs are poor candidates for Sustained release preparations. Drugs with long half-life, more than 8 hrs, are also generally not used in sustaining forms, since their effect is already extended [19].

5) Side Effects and Safety Considerations: -There are very few drugs whose specific therapeutic concentrations are known. Instead, a therapeutic concentration range is listed, with increasing toxic effects expected above this range and a falloff in desired therapeutic response observed below the range.

The most widely used measure of the margin of safety of a drug is its therapeutic index (TI).

$$TI = TD_{50} / ED_{50}$$

Where

TD_{50} = median toxic dose

ED_{50} = median effective dose

For very potent drugs, whose therapeutic concentration range is narrow, the value of TI is small. In general, larger the value of TI, the safer the drug. Drugs with very small value of TI usually are poor candidates for formulation into controlled-release product. A drug is considered to be relatively safe if its TI value exceeds 10.

6) Dose Size: -Since a controlled-release system is designed to alleviate repetitive dosing, it naturally will contain a

greater amount of drug than a corresponding conventional dosage form. For those drugs requiring large conventional doses, the volume of the Sustained dose may be so large as to be impractical or unacceptable, depending on the route of administration. The same may be true for drugs that require a large release rate from the controlled-release system, e.g., drugs with shorter half-life. For oral route, the volume of the product is limited by patient acceptance [20].

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 for mula 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 millilitre. Bulk density was calculated using in the following formula.

Bulk density =W/V

- 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.

Tapped density=W/V

- 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.

Compressibility index=100XV0-Vf / V0

- Hausner ratio: -Hausner Ratio was calculated using in the following formula [21].

Hausner Ratio=V0/Vf

Characteristics of granules of Amisulpride OD Tablets formulation (table 1).

Table no 1- Characteristics of granules of Amisulpride OD Tablets formulation

S.N0.	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	0.67%
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

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 (table 2) 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- membrane. The absorbance was measured with UV spectrometer after suitable dilution [22].
- 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 [23].

Table no. 2-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)	19hour 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 20sec	101.13
6	AM6	990 ±5%	99.10(2.9)	23 hour 40sec	101.11

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. 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 forAM_6 achieves the acceptance criteria for Dissolved in 24 hours in dissolution medium.

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