Research Article

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PREFORMULATION STUDY OF ARIPIPRAZOLE FOR FORMULATION AND DEVELOPMENT OF NEWER ANTIPSYCHOTIC FORMULATION

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ABSTRACT

Aripiprazole is an antipsychotic medication, works by changing the actions of chemicals in the brain. It is used to treat the symptoms of psychotic conditions such as schizophrenia and bipolar disorder (manic depression). In order to formulate a newer aripiprazole immediate release tablet of strength 30mg we performed the preformulation study for the active pharmaceutical ingredient. Based on the market product information, drug-excipient compatibility study (physical and chemical characteristics) was performed using different excipients of choice for the formulation to determine the compatibility of the excipient with drug at accelerated conditions (for 4 weeks - 40°C / 75% relative humidity in polybag and for 2 weeks – 60°C in a glass vial). Based on the drug – excipient compatibility study and the reference product information leaflet, the excipients were selected for the formulation development. The results obtained were satisfactory and within the specified limits. The selected excipients showed good compatibility with the aripiprazole. The drug -excipient compatibility study was found to be useful for formulation and development of newer aripiprazole immediate release tablet.

Keywords: Aripiprazole, atypical antipsychotics, schizophrenia, preformulation, drug-excipient compatibility, immediate release tablets.

INTRODUCTION

Aripiprazole is an antipsychotic medication, works by changing the actions of chemicals in the brain[1,2,3]. It is used to treat the symptoms of psychotic conditions such as schizophrenia and bipolar disorder (manic depression)[4,5].

Aripiprazole possess a different mechanism of action which is different from other FDA - approved atypical antipsychotics approved by Food and Drug Administration[6,7,8]. Instead of acting as an antagonist at D_2 receptor it acts as a partial agonist at the D2 receptor[9,10]. It also acts as the partial agonist at the 5-HT_1A receptor but exhibits the role of the antagonist at 5-HT_2A receptor similar to that of the other atypical anti-pshycotics[11]. Aripiprazole also possess high affinity towards 5-HT_7 receptor (acts as antagonist) and 5-HT_2C receptor (acts as a partial agonist)[12,13]. Its action on the 5-HT_7 receptor and 5-HT_2C receptor is found to be the main cause of weight gain of the patient during the treatment period[14]. Aripiprazole also possess moderate affinity for histaminergic, α-adrenergic, dopaminergic receptors and serotonin transporter[15]. It has a very less affinity for muscarinic acetyl choline receptors[16]. The main aim and objective of this work is to perform the drug-excipient compatibility study and selection of appropriate excipients to formulate a stable and robust formulation of aripiprazole immediate release tablet 30mg, which is used in the treatment of schizophrenia and bipolar disorders.

MATERIALS AND METHODS

The drug-excipient compatibility study and selection of excipients for the newer anti-psychotic formulation was based on the marketed product profile of aripiprazole available in five different strengths namely 5 mg, 10 mg, 15 mg, 20 mg and 30 mg[17,18].

Accelerated compatibility study

Based on the market product information, drug-excipient compatibility study was performed using different excipients of choice in the formulation to determine the compatibility of the excipient with drug at accelerated conditions. The study was conducted by preparing homogeneous mixture of excipient with drug, filled in glass vial and low density poly ethylene (LDPE) bags. Glass vial and LDPE bags were exposed at 40°C ± 2°C / 75±5 % RH for 4 weeks, glass vials at 60°C for 2 weeks. Initial samples and the samples exposed at 40°±2°C / 75±5 % RH (4th week, polybag) and 60°C ±2°C (2nd week, glass vial) were analyzed for the physical and the chemical characteristics. Based on the drug-excipient compatibility study data the excipients were selected.

Based on the literature review of the excipients and the formulation requirements for aripiprazole the drug and excipient ratios were selected as shown in the table 1.

Selection of excipients

Based on the drug – excipient compatibility study and the reference product information leaflet, the excipients were selected for the formulation development. The selected excipients are lactose monohydrate, corn starch, ferric oxide red, hydroxypropyl cellulose, microcrystalline cellulose, talc, colloidal silicon dioxide and magnesium stearate. These excipients were used in the selection of manufacturing process for the selected anti-psychotic drug through trials.

Table 1: List of drugs – excipients and their ratio

S.NO	DRUG + EXCIPIENTS	RATIO
1	API	----
2	D + Lactose monohydrate	1: 5
3	D + Corn Starch	1: 1
4	D + Hydroxypropyl cellulose	1: 0.2
5	D + Ferric oxide red	1: 0.01
6	D + FD&C Blue 2 Aluminium Lake	1: 0.01
7	D + Microcrystalline Cellulose	1: 2
8	D + Talc	1: 0.5
9	D + Colloidal silicon dioxide	1: 0.1
10	D + Magnesium Stearate	1: 0.2
11	D + Klucel-LF	1: 0.5
12	D + Starch 1500	1: 5
13	D + Ac-di-sol	1: 1
14	D + Crospovidone	1: 1

Table 2: Physical characteristics of drug-excipient mixture

Composition	**Initial description**	**Observation**	
		4^{th} week 40^0C /75%RH Polybag	2^{nd} week 60^0C Glass Vial
API	Off-white crystalline powder	No Change	No Change
D + Lactose monohydrate	White colour fine powder	No Change	No Change
D + Corn Starch	White colour fine powder	No Change	No Change
D + Hydroxypropyl cellulose	Off-white fine powder	No Change	No Change
D + Ferric oxide red	Brick red colour fine powder	No Change	No Change
D + FD&C Blue 2 Aluminium Lake	Blue colour fine powder	No Change	No Change
D + Microcrystalline Cellulose	White colour fine powder	No Change	No Change
D + Talc	White colour fine powder	No Change	No Change
D + Aerosil	White colour fine powder	No Change	No Change
D + Magnesium Stearate	White colour fine powder	No Change	No Change
D + Klucel-LF	Off-white fine powder	No Change	No Change
D + Starch 1500	White colour fine powder	No Change	No Change
D + Ac-di-sol	White colour fine powder	No Change	No Change
D + Crospovidone	White colour fine powder	No Change	No Change

Table 3: Chemical characteristics of drug-excipient mixture

Drug + Excipient	**% w/w Total impurity**		
	Initial	**4^{th} week 40^0C/75%RH Polybag**	**2^{nd} week 60^0C Glass Vial**
API	0.160	0.140	0.150
D + Lactose monohydrate	0.160	0.130	0.160
D + Corn Starch	0.370	0.140	0.320
D + Hydroxypropyl cellulose	0.160	0.130	0.170
D + Ferric oxide red	0.360	0.130	0.190
D + FD&C Blue 2 Aluminium Lake	0.160	0.130	0.180
D + Microcrystalline Cellulose	0.150	0.130	0.200
D + Talc	0.160	0.120	0.180
D + Colloidal silicon dioxide	0.180	0.130	0.170
D + Magnesium Stearate	0.160	0.140	0.170
D + Klucel-LF	0.160	0.130	0.160
D + Starch 1500	0.170	0.150	0.180
D + Ac-di-sol	0.160	0.130	0.150
D + Crospovidone	0.160	0.150	0.190

Table 4: Excipients selected for formulation and development

S.No	**Ingredients**	**Functional Category**
1	Lactose monohydrate	Diluent
2	Corn Starch	Disintegrant
3	Ferric oxide red	Colorant
4	Hydroxypropyl cellulose	Binder
5	Microcrystalline cellulose	Diluent
6	Talc	Glidant
7	Colloidal silicon-di-oxide	Glidant
8	Magnesium stearate	Lubricant

RESULTS

Accelerated compatibility study

The active pharmaceutical ingredient and the respective drug-excipient mixture were analyzed for the physical and the chemical characteristics and the results are presented in the table 2 and table 3.

Selection of excipients

Based on the drug – excipient compatibility study and the reference product information leaflet, the excipients selected for the formulation development of aripiprazole immediate release tablet of strength 30mg is presented in the table 4.

DISCUSSION

Though there are several methods for determination of drug-excipient compatibility study the study of physical and chemical characteristics of drug excipient mixture and selection of excipients based on this study yielded conclusive evidence on the selection of appropriate excipients.

Based on the analysis of the drug-excipient mixture, it was concluded that there was no change in physical characteristics, such as color change at 4^{th} week 40^0C / 75% RH in polybag and at 2^{nd} week of 60^0C at glass vial.

Based on the chemical evaluation data, it was found that there was no significant change observed in the chemical characteristics indicating drug – excipient compatibility.

The results of the drug and drug-excipient compatibility study contributed significantly for the appropriate selection of excipients for the formulation and development of selected antipsychotic formulation

CONCLUSION

The active pharmaceutical ingredient (aripiprazole) and drug-excipient mixture was evaluated for their compatibility based on the evaluation of physical and chemical characteristics on accelerated stability conditions. The results obtained were satisfactory and within the specified limits. The results of the study were found to be useful in the formulation and development of newer aripiprazole immediate release tablets of strength 30mg.

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