FORMULATION AND EVALUATION OF AMISULPRIDE ORODISPERSIBLE TABLET

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Abstract

Orodispersible dosage forms have lured the market for a certain section of the patient population which includes dysphagia, bed ridden, psychic, and geriatric patients. Moreover Orodispersible tablets shows increased bioavailability as compared to conventional dosage forms. Amisulpride is a psychotropic agent belonging to the chemical class of benzamide derivatives. At low doses, it enhances dopaminergic neurotransmission by preferentially blocking presynaptic dopamine D2/D3 auto receptors. The tablets were prepared by using direct compression method, and drug solubility is enhanced by solid dispersion. Formulation were prepared by using different superdisintegrant, combination of different superdisintegrant and effect of hydrophilic lubricant was studied and evaluated pre and post compression parameters. Tablets were evaluated for content uniformity, Disintegration time, wetting time, hardness, friability and *In-vitro* dissolution studies. More than 90% of drug was released from almost all the formulations within 10 min. Formulation C4 containing Sodium starch glycolate (4.5%), Crospovidone (2.5%) and crosscarmellose sodium (3.5%), was having disintegration time 24 seconds, wetting time 18 seconds, hardness 3.4Kg/cm^2 and *in vitro* drug release of 99.96% in pH 6.8. Based on this data C4 was found to be the best formulation. Further formulations were subjected to accelerated stability studies. Tablets showed no appreciable changes with respect to disintegration and dissolution profiles. Results of this study indicate among the superdisintegrants tried, combination of superdisintegrant gave the best result.

Key word: Orodispersible tablet, Amisulpride, super disintegrant, psychotropic agent

Introduction:

Amisulpride is a substituted benzamide derivative structurally related to sulpiride. It belongs to the second-generation antipsychotic drug that preferably binds to dopamine D2 /D3 receptors in limbic rather than striatal structures [1]. Amisulpride is indicated for the treatment of acute and chronic schizophrenia with prominent positive and/or negative symptoms. Orodispersible tablet system can be defined as a tablet that disintegrates and dissolves rapidly in saliva within few seconds without need of drinking water or chewing [2]. Orally disintegrating tablets have better patient acceptance and compliance and may offer improved biopharmaceutical properties, efficacy and increased bioavailability compared with conventional oral dosage Forms [1]. They obviate the problem associated with conventional dosage forms, it has benefits like desired hardness, dosage uniformity, extremely easy administration and since no water is required for swallowing these tablets are suitable for geriatric, pediatric and travelling patients. These tablets display a fast and spontaneous de-aggregation in the mouth, soon after it comes in contact with saliva, dissolving the active ingredient and allowing absorption through all possible membrane it comes in contact during deglutition [3].

Amisulpride ODT which when placed in the tongue disintegrates or dissolves rapidly in the saliva without the need of drinking water. As tablet disintegrates in the mouth, this could enhance the clinical effect of the drug through pregastric absorption from the mouth, pharynx and esophagus. This leads to an increase in bioavailability by avoiding first pass liver metabolism [4]. The drug releases from the ODT due to the action of super disintegrates like crosscarmellose sodium and Sodium Starch Glycolate and sublimating agents like Camphor and Ammonium Bicarbonate in the formulation [5]. Superdisintegrants provide quick disintegration due to combined effect of swelling and water absorption by the formulation. As an effect of swelling of superdisintegrant, the wetted surface of the carrier increases, which promotes wettability and dispersibility of the system and thereby enhance the disintegration and dissolution. While sublimating agents aids by forming porous structure on tablet's surface. Hence ODT of Amisulpride has been developed by two methods i.e. direct compression and sublimation with the goal of speeding absorption and rapid onset of effect compared to standard Amisulpride tablets. The basic approach used in the present study for the development of the fast dissolving tablet is use of superdisintegrants like crosscarmellose sodium and sodium starch glycolate to ease faster disintegration and sublimable agents like ammonium carbonate and camphor to generate porous structure by sublimation of volatile oil [6]. Amisulpride is given to Psychotropic patients which are unable to take the medicine, so Amisulpride Orodispersible tablet are prepared [7].

Materials and Method:

Material

Amisulpride was gifted by Sun Pharma Silvassa, PEG 6000 (Sudhachem Pvt Ltd.), Mannitol (Shandorytiani Pharma Pvt Ltd), Hydrochloric acid (Rankem,Mumbai.), Sodium starch glycolate (Rosewell Industry, Mumbai), Crospovidone (Sinobright Dev United.), Cross carmellose sodium (Roswell Industry, Mumbai), Vanillin (Analab fine chemicals, Mumbai), Magnesium Stearate (Nikita chemicals, Vapi), Talc (Loba Chemie Pvt. Ltd.), Potassium dihydrogen phosphate (Rankem,Mumbai), Disodium hydrogen phosphate (Rankem,Mumbai), Sucralose (Kashyap sweetener Ltd, Mumbai.), Isopropyl alcohol (Shanghai Sunflower Technology Development, Mumbai), Sodium hydroxide (Rankem, Mumbai), Potassium chloride (Rankem, Mumbai). All ingredients and solvent was use analytical grade.

Methods

Preparation of Amisulpride ODT by direct compression method

Amisulpride orodispersible tablet was prepared by direct compression method. All the ingredients were weighed and passed through sieve no #60 separately and collected and then were mixed, the solid dispersed drug was weighed and added in the above mixture, magnesium stearate and talc were added and then mixed in geometrical fashion, ensuring proper mixing of all the ingredients .All ingredient were passed through sieve no #60 separately and weigh all ingredient as per table -1 and mixed well except magnesium stearate and talc for 10 min. Mg stearate and talc were added on mixture in geometrical fashion ensuring proper mixture of all ingredients. The tablets were compressed using 11 mm punch keeping the total tablet weight constant at 350 mg with the help of mannitol, using 32 stations rotary tablet compression machine (Hardik eng).

Table.1: Formula for Orodispersible tablet.

Ingredient	F0	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Complex	200	200	200	200	200	200	200	200	200	200	200
Sodium starch glycolate	-	8.75	-	-	12.25	-	-	15.75	-	-	-
Crospovidone	-	-	8.75	-	-	12.25	-	-	15.75	-	-
Crosscarmellose sodium	-	-	-	8.75	-	-	12.25	-	-	15.75	15.75
Sucralose	3	3	3	3	3	3	3	3	3	3	3
Vanillin	1	1	1	1	1	1	1	1	1	1	1
Mg stearate	5	5	5	5	5	5	5	5	5	5	-
Talc	5	5	5	5	5	5	5	5	5	5	-
Sodium lauryl sulphate	-	-	-	-	-	-	-	-	-	-	3.5
Mannitol	136	127.25	127.25	127.25	123.75	123.75	123.75	120.25	120.25	120.25	126.75
Total	350	350	350	350	350	350	350	350	350	350	350

Table 2: Formula for combination of Orodispersible tablet.

Ingredient	C1	C2	C3	C4
Complex	200	200	200	200
Sodium starch glycolate	15.75	15.75	-	15.75
Crosscarmellose sodium	12.25	-	12.25	12.25
Crospovidone	-	8.75	8.75	8.75
SUCRELOSE	3	3	3	3
Vanillin	1	1	1	1
Mg stearate	5	5	5	5
Talc	5	5	5	5
Mannitol	108	111.5	115	99.25
Total	350	350	350	350

Evaluation:

Amisulpride orodispersible tablets prepared by direct compression were subject to following physical evaluation.

1. Dimensions

The thickness and diameter of the tablets was determined using a Vernier caliper. Five tablets from each formulation were used and average values were calculated [11].

2. Weight variation

Weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average weight [10].

3. Friability

The friability (F) of a sample of 20 tablets was measured using

Roche friabilator ((ERWEKA, Germany). Twenty tablets were weighed, rotated at 25 rpm for 4 min. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated. Friability less than 1% was considered acceptable [10].

$$\% \text{ Friability } = \frac{\text{Initial Wt} - \text{Final Wt.}}{\text{Initial wt.}} \times 100$$

4. Hardness

The tablet hardness is the force required to break a tablet in a diametric compression force. Erweka hardness tester (Erweka, Germany) was used in this study. This tester applies force to the tablet diametrically. The test was performed on six tablets and the average was calculated [11].

5. *In-vitro* Disintegration Studies

Tablet was placed in a beaker containing 20 ml of distilled water at 37 ±0.5 °C. Time for complete disintegration of the tablet was measured in triplicate [10].

6. Wetting Time

The wetting time of the tablets can be measured using a simple procedure. A filter paper of 10 cm diameter was placed in a Petri dish with a 10 cm diameter. One milliliter of water containing amaranth, a water soluble dye, was added to Petri dish. A tablet was carefully placed on the surface of the filter paper. The time required for water to reach the upper surface of the tablet was noted as a wetting time. Three determinations were performed [11].

7. Tablet Assay

Ten tablets were accurately weighed and finely powdered. A weight equivalent to 100 mg of Amisulpride was transferred to a 100 ml volumetric flask. To it, 50 ml of 0.1 N HCl was added and shaken for 1 hour to dissolve drug. The solution was filtered and residue was washed with 25 ml of 0.1 N HCl. The washing obtained was added to initial filtrate and volume was made upto 100 ml with 0.1 N HCl. From above solution 1 ml of stock solution was diluted to 10 ml. The drug content was determined spectrophotometrically at 225.5nm [8].

8. *In-vitro* Dissolution Studies

Dissolution studies were carried out for all the formulation combinations in triplicate, employing USP XXIII paddle method (Apparatus 2) using pH 6.8 as the dissolution medium (900 ml) at 50 rpm and 37 ± 0.5ºC. An aliquot of sample was periodically withdrawn at suitable time intervals and volume replaced with equivalent amounts of fresh dissolution medium. The samples were analyzed spectrophotometrically at 225.5nm and 226.5 nm [14].

9. Stability studies

Stability studies on the best formulation were carried out to determine the effect of presence of formulation additives on the stability of the drug and also to determine the physical stability of the formulation under accelerated storage conditions. The tablets were stored in an aluminum foil and subjected to –

- Elevated temperature and humidity conditions of 40 ± 2ºC/ 75 ± 5 % RH
- A control sample was placed at an ambient condition.

The samples were withdrawn at the end of 15 days and 30 days and evaluated for drug content, Disintegration Time and *In-vitro* drug releases [12-13].

RESULT AND DISCUSSON:

Amisulpride Orodispersible tablet were prepared by direct compression method being the most simple and the economic technique. The aim of study to optimize Orodispersible tablet for developing a dosage form avoid first pass metabolism by dissolving and disintegrating the tablet in saliva within few second with the addition of superdisintegrant and their various combination.

Hardness of the tablet was found to be between 3.1-4.2 kg/cm^2. Thickness of tablets was found to be 3.01-3.11 mm±1.38 % CV. Diameter of tablets was found to be 10-10.01 mm. Percentage Friability of all formulation was found to be 0.22-0.83% which is less than 1% indicating good mechanical characteristic. The average weight of tablets was found to be 344.2-348.45 mg.

The Physical evaluation of tablet prepared by combination of superdisintegrant as shown in Table 4. Hardness was found to be between 3.3-4.2 kg/cm2.Thickness of tablets was found to be 3.01-3.12 mm.0.74±0.14 % CV. Diameter of tablets was found to be 10-10.01 mm.0.05 % CV. Friability of tablets was found to be 0.30-0.71% which passes the test as per Indian Pharmacopoeia specification. The average weight of tablets was found to be 347.25-348.7 mg.17.36 mg±17.42 mg which passes the weight uniformity test as per Indian Pharmacopoeia specification. Formulation C4 containing Sodium starch glycolate (4.5%), Crospovidone (2.5%) and crosscarmellose sodium (3.5%), was having a hardness of 3.4±0.19 (kg/cm2) and friability of 0.30% is a better formulation.

Table 3: Physical Evaluation of tablets

Formulation	Weight variation (mg)	Hardness (Kg/cm^2)	Diameter (mm)	Thickness (mm)	Friability (%)
F0	347±17.35	3.6±0.28	10±0.05	3.11±0.14	0.24
F1	348.45±17.42	3.3±0.57	10±0.05	3.1±0.18	0.83
F2	347.3±17.36	3.3±0.57	10±0.05	3.03±0.9	0.22
F3	347.3±17.36	3.8±0.28	10±0.05	3.01±0.74	0.31
F4	346.25±17.31	4.2±0.28	10.01±0	3.06±1.37	0.72
F5	347.6±17.38	3.8±0.28	10.01±0	3.05±1.16	0.64
F6	345.57±17.27	3.3±0.57	10.01±0	3.04±1.38	0.55
F7	344.2±17.21	3.1±0.66	10.01±0	3.05±0	0.33
F8	348.1±17.40	3.5±0.565	10.01±0	3.11±0.14	0.62
F9	346.7±17.33	3.4±0.19	10.01±0	3.1±0.18	0.53
F10	347.3±17.36	3.3±0.57	10±0.05	3.0±0.74	0.24

Table 4: Physical Evaluation of tablets prepared by combination of superdisintegrants

Formulation	Weight variation	Hardness (Kg/cm2)	Diameter (mm±S.D)	Thickness (mm±S.D)	Friability (%±S.D)
C1	348.7±17.43	3.3±0.57	10.01±0	3.12±0.14	0.52
C2	348.45±17.42	3.8±0.28	10±0.05	3.1±0.18	0.56
C3	347.25±17.36	4.2±0.28	10.01±0	3.04±1.38	0.71
C4	347.4±13.37	3.4±0.19	10.01±0	3.01±0.74	0.30

In-vitro Disintegration test

Disintegration time of different formulation is shown in table 5. The value was found to be in range of 29-200 seconds. Formulation F0 shows highest disintegration time i.e. 200 seconds as it does not contain any superdisintegrant agent. Formulation F1, F4 and F7 contain Sodium starch glycolate as superdisintegrant having concentration 2.5%, 3.5% and 4.5% has disintegration time as 165, 55 and 43 seconds respectively. Formulations F2, F5 and F8 contains Cross Povidone as superdisintegrant having concentration 2.5%, 3.5% and 4.5% has disintegration time as 105, 49 and 40 seconds respectively. Formulations F3, F6 and F9 contains Crosscarmellose Sodium as superdisintegrant having concentration 2.5%, 3.5% and 4.5% has disintegration time as 107, 42 and 31 respectively . Formulation F10 contains Crosscarmellose sodium and Sodium lauryl sulphate as a hydrophilic lubricant with least disintegration time of 29 seconds.

Effect of water soluble Lubricant in Disintegration test

Disintegration time of different formulation prepared by combination of superdisintegrant is shown in table 6. The value was found to be in range of 24-33 seconds. Formulation C1 contains combination of Sodium starch glycolate and Crosscarmellose sodium having concentration 4.5% and 3.5% has disintegration time as 33 seconds. Formulation C2 contains combination of Sodium starch glycolate and Crospovidone having

concentration 4.5% and 2.5% has disintegration time as 35 seconds. Formulation C3 contains combination of Crosscarmellose sodium and Crospovidone having concentration 3.5% and 2.5% has disintegration time as 30 seconds. Formulation C4 contains combination of all three superdisintegrant i.e. SSG, CCS and CP having concentration 4.5, 3.5% and 2.5% has disintegration time as 24 seconds.

Wetting time

Wetting time of different formulation is shown in table 5. The value was found to be in range of 17-102 seconds. Formulation F0 shows highest wetting time i.e. 102 seconds as it does not contain any superdisintegrant agent. Formulation F1, F4 and F7 contain Sodium starch glycolate as superdisintegrant having concentration 2.5%, 3.5% and 4.5% has wetting time as 90, 43 and 33 seconds respectively. Formulations F2, F5 and F8 contains Cross Povidone as superdisintegrant having concentration 2.5%, 3.5% and 4.5% has wetting time as 81, 37 and 28 seconds respectively. Formulations F3, F6 and F9 contains Crosscarmellose Sodium as superdisintegrant having concentration 2.5%, 3.5% and 4.5% has wetting time as 99, 26 and 23 respectively . Formulation F10 contains Crosscarmellose sodium and Sodium lauryl sulphate as a hydrophilic lubricant with least wetting time of 17 seconds.

Wetting time of different formulation prepared by combination of superdisintegrant is shown in table 6. The value was found to be in range of 18-25 seconds. Formulation C1 contains combination of Sodium starch glycolate and Crosscarmellose sodium having concentration 4.5% and 3.5% has wetting time as 24 seconds. Formulation C2 contains combination of Sodium starch glycolate and Crospovidone having concentration 4.5% and 2.5% has wetting time as 25 seconds. Formulation C3 contains combination of Crosscarmellose sodium and Crospovidone having concentration 3.5% and 2.5% has wetting time as 20 seconds. Formulation C4 contains combination of all three superdisintegrant i.e. SSG, CCS and CP having concentration 4.5, 3.5% and 2.5% has wetting time as 18 seconds. Thus it is clear that as concentration of superdisintegrant increases, the wetting time of tablet decrease.

Drug content

The drug content of Amisulpride of different formulation are shown in table 5.The value was found to be between 92.65-99.77% for Amisulpride which passes the test as per standard limit (90-110%).

Table 5: In-vitro Disintegration time, wetting time and Tablet assay of all formulations

Formulation	Disintegration time(seconds)	Wetting time (seconds)	Tablet assay (%)
F0	200	102	92.65
F1	165	90	97.89
F2	105	81	97.67
F3	107	99	96.99
F4	55	43	96.57
F5	49	37	98.3
F6	42	26	98.65
F7	43	33	99.1
F8	40	28	98.7
F9	31	23	99.77
F10	29	17	99.06

Table 6: In-vitro Disintegration time, wetting time and Tablet assay of tablets prepared by combination of superdisintegrants

Formulation	Disintegration time(seconds)	Wetting time (seconds)	Tablet assay (%)
C1	33	24	95.48
C2	35	25	96.17
C3	30	20	98.18
C4	24	18	99.80

***In- vitro* dissolution profile of Amisulpride orodispersible tablet in phosphate buffer pH 6.8**

Dissolution profile of all formulation is shown in figure 1, 2, 3 4. Dissolution study was carried out in phosphate buffer pH 6.8 media, using USP Apparatus type-2 (paddle), at 37ºC temperature. Dissolution time of 10 min was chosen because all the drug was released within 10 minutes. Formulation F0 does not content any superdisintegrant and has a drug release of 60.69 % within 10 minutes. Formulation F1 to F9 contain varying concentration of superdisintegrant and hydrophobic lubricant and showed *In-vitro* drug release of 91.94 % to 101.31 % respectively. Formulation F10 contain cross carmellose sodium and hydrophilic lubricant as sodium lauryl sulphate and showed *In-vitro* drug release of 98.01% after 10 minute. Thus be said that hydrophilic lubricant sodium lauryl sulphate showed no effect on drug release.

Dissolution profile of different formulation prepared by combination of superdisintegrant is shown in figure 5. Formulation C1 contains combination of Sodium starch glycolate and Crosscarmellose sodium having concentration 4.5% and 3.5% has dissolution rate of 95.02%. Formulation C2 contains combination of Sodium starch glycolate and Crospovidone having concentration 4.5% and 2.5% has dissolution rate of 91.87%. Formulation C3 contains combination of Crosscarmellose sodium and Crospovidone having concentration 3.5% and 2.5% has dissolution rate of 96.78%. Formulation C4 contains combination of all three superdisintegrant i.e. SSG, CCS and CP having concentration 4.5, 3.5% and 2.5% has dissolution rate of 99.96%.Now from the above value, the formula C4 has highest dissolution rate 99.96% compare to the C1 of 95.2% , and C3 of 96.78%.Formulation C2 has least dissolution rate of 91.87%.

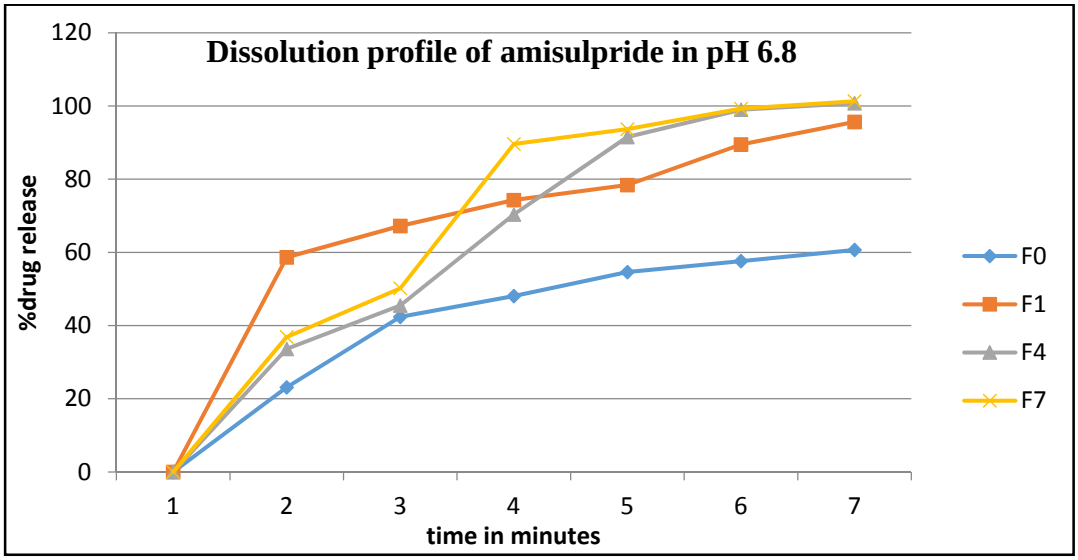

Figure 1: % drug release of F0, F1, F4, F7 (Sodium starch glycolate)

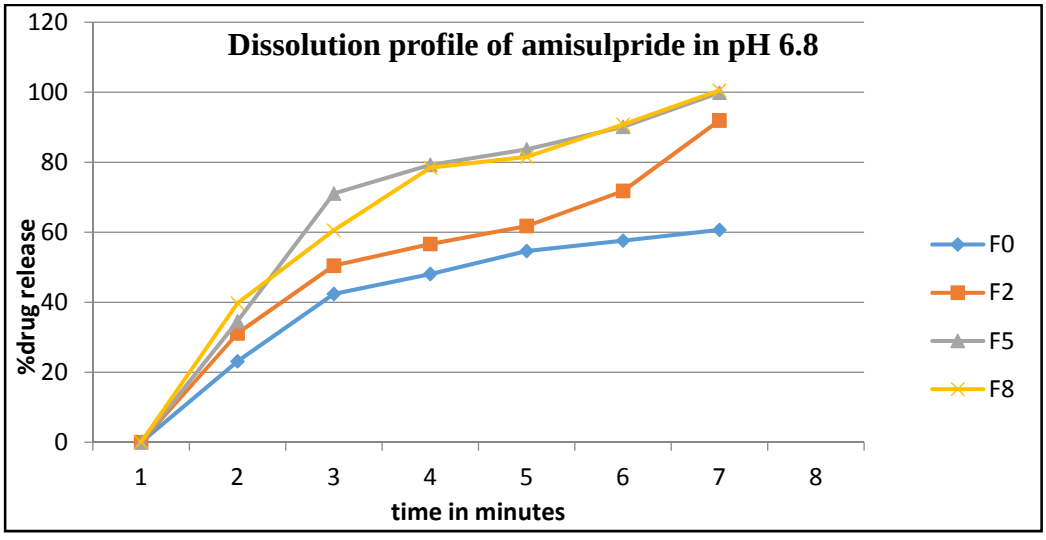

Figure 2:% drug release of F0, F2, F5, F8 (Crospovidone)

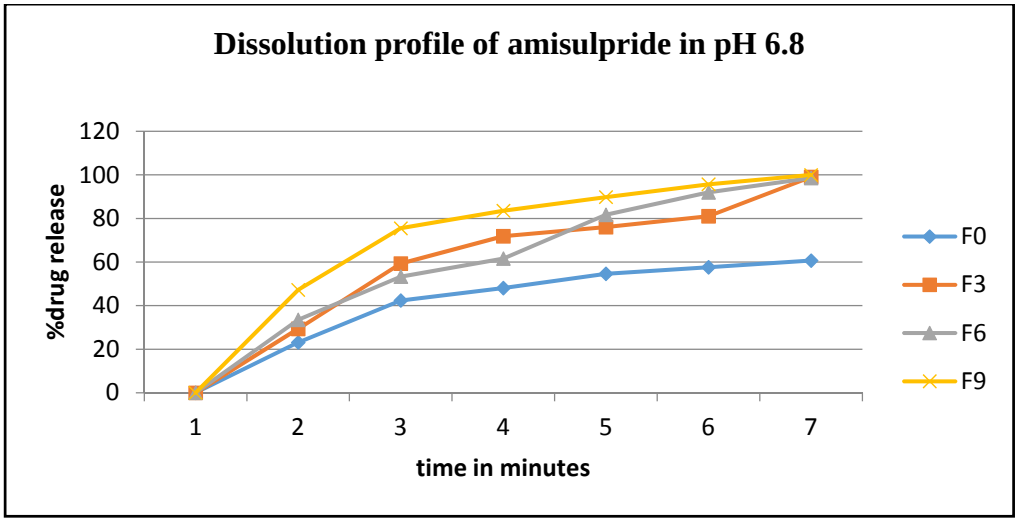

Figure 3: % drug release of F0, F3, F6, F9 (Crosscarmellose sodium)

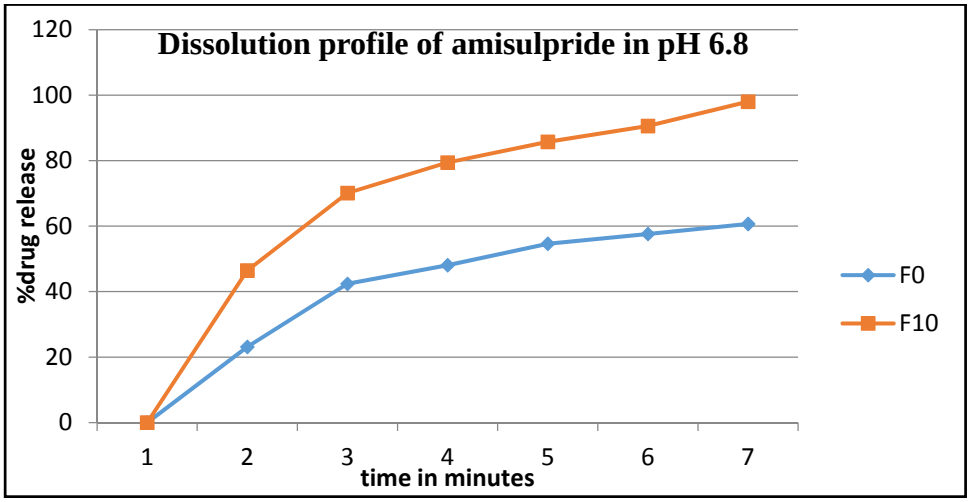

Figure 4: % drug release of F0, F10 (hydrophilic lubricant)

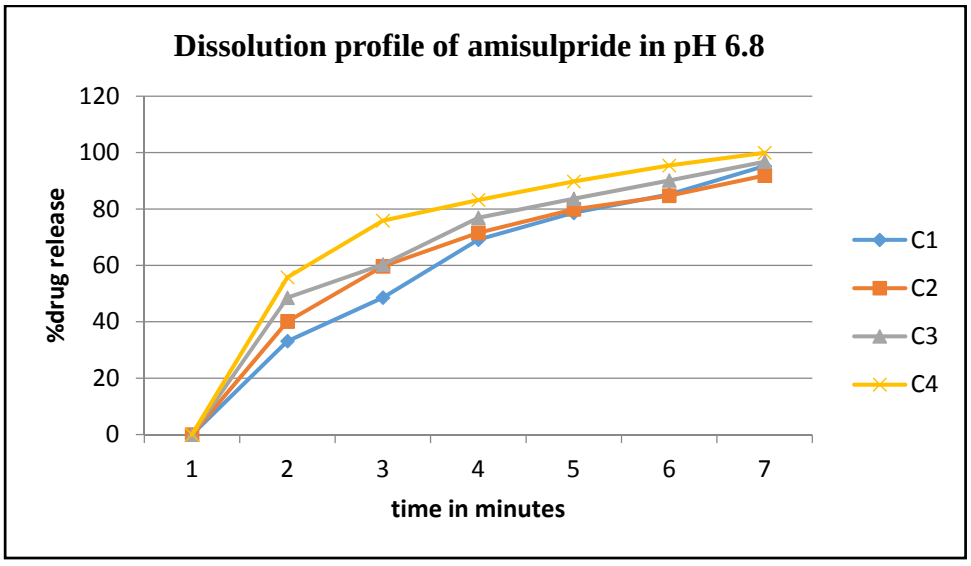

Figure 5: Percentage drug release of formulations prepared by combination of superdisintegrants in 6.8 pH

Stability Studies

The stability studies of the best formulation (C4) of Orodispersible tablets revealed that no significant changes in the physical parameters when stored at temperature and humidity conditions of 40 ± 2°C/75 ± 5 % RH respectively and at room temperature. No significant reduction in the content of the active drug was observed over a period of 15 and 30 days .The optimum formulation did not show any significant change in disintegration time, % release after 10 minutes and drug content when kept at different condition and periods. Stability studies of promising formulation indicates that there is no significant change in the drug content and in-vitro dispersion time. Also by comparing FTIR spectra of drug and excipient, the identified peaks for the drug remains unchanged which concludes compatibility between the drug and excipients.

Conclusion

From the study, it can be concluded that direct compression methods could be applied effectively in preparing Amisulpride ODTs with better disintegration and drug release properties. The prepared ODTs disintegrate within few seconds without need of water. *In -vitro* disintegration test revealed that the tablets prepared by using combination of super disintegrating agent like sodium starch glycolate, crospovidone and crosscarmellose sodium showed faster disintegration. The dissolution studies confirmed that tablets prepared with combination showed faster drug release. Formulation C4 was found to be the best ODTs among all, in which *In-vitro* disintegration time and *in vitro* drug release was found to be 24 sec and 100.01% drug release within 10 mins.

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