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Preparation Of Sustain Release Antipsychotic *(Amisulpride)* Tablet by *Bilayer GRDDS Concept*

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ABSTRACT

For decades an acute or chronic illness is being clinically treated through delivery of drugs to the patients in form of some pharmaceutical dosage forms,in that one of that is *bilayer GRDDS(Gastro Retentive Drug Delivery system) tablets.*in that system those antipsychotic drugs like Amisulpride half-life 11,are retarded in Gastric fluid with the help of different polymers like (Kollidone SR, Cross Povidone) and excipients (Sodium-bi-Carbonet) which provide the swelling action to the dosage form Because of the swelling action the tablet dissolution will be late so that absorption of the drug will be decreses and duration of action of the drug is increases and sustained. 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 Povidone, Aerosil, Avesil 101, 112, 102, Sodium B i-carbonate, Poly vinyl pyrollidone K-30, Carbopol with varying excipients Six bilayer for mulations AM_1-AM_6 were prepared by compressing both Instant Release (IR) and Sustained Release (SR) granules.

KEYWORDS : Sustain release, Bilayer GRRDS, Kollidone SR, Sodium-bi-Carbonet.

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INTRODUCTION

Greater attention has been focused on development of sustained or controlled release drug delivery systems with concomitant recognition of the therapeutic advantages of controlled drug delivery. Controlled drug delivery systems have been introduced to overwhelm the drawback of fluctuating drug levels associated with conventional dosage forms[1]. 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 purpose[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, H1histaminergic or cholinergic receptors[2,3]. 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. In the present work, hydrophilic matrix materials such as hydroxyl-propyl methylcellulose are used. Formulations AM_1 to AM_{12} are prepared by varying excipients.Microcrystalline Cellulose, Hydroxy Propyl methylcellulose(H.P.M.C), Talc, Magnesium Stearate, IsoPropyl alcohol, Xanthan Gum, Kollidone, Cross Povidone , Aerosil, Avesil 101,112,102 ,Sodium Bi-carbonate, Poly vinylpyrollidone K- 30, Carbopol are used for formulation[4,5].

MATERIALS AND METHODS

The following materials of Pharma grade or the best possible Laboratory Reagent (LR) were used as supplied by the manufacturer.

Table 1: List of materials used in the experiment

Materials used in the present study			
Sr. no.	**Materials used**	**Grade**	**Manufacturer**
1	Amisulpride	Pharma Grade	Anjan drugs Pvt.Ltd.,Chennai
2	Microcrystalline Cellulose	LR	Shreeji chemicals, Mumbai
3	Ferrous Red Oxide	LR	Shreeji chemicals, Mumbai
5	H.P.M.C	LR	Mittal polymer, Bombay
6	Talc	LR	S d fine chemical Ltd, Mumbai
7	Magnesium Stearate	LR	S d fine chemical Ltd, Mumbai
8	Iso Propyl alcohol	LR	S d fine chemical Ltd, Mumbai
9	Xanthenes Gum	LR	Mittal polymer, Bombay
10	Kollidone SR	LR	Mittal polymer, Bombay
11	Cross Povidone	LR	Mittal polymer, Bombay
12	Sodium Bi- carbonate	LR	Qualigens fine chem., Mumbai
13	Poly vinyl pyrollidone K-30	LR	Mittal polymer, Bombay
14	Carbopol	LR	Mittal polymer, Bombay

EVALUATION OF GRANULES[6,7,8]

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 milliliter. Bulk density was calculated using in the following formula.

Bulk density =W/V_0

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 fo rmula.

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.

Compressibility index=100XV0-Vf / V0

Hausner ratio

Hausner Ratio was calculated using in the following formula.

Hausner Ratio=V0/Vf

EVALUATION OF TABLETS[9,10]

Weight variat ion 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 0.45µ 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 37^0 C ± 0.5^0 C. The drug release at different time intervals was measured by UV- visible spectrophotometer.

FORMULATION STRATEGY OF AMISULPRIDE OD (ONCE DAILY)TABLET

- Amisulpride is absorbed well in the upper GIT, thus a Gastro retentive dosage form would give better bioavailability – Published patent of Aventis describes GRD based on CO2 generating system.
- Also, prolonged release over the entire length of GIT is not suitable for Amisulpride because it is poorly absorbed at the colonic level and is a substrate of P-glycoprotein outflow.
- So, for Amisulpride OD to take feasibility trial batch on Bi-layer concept, so the SR Part and IRPart maintain the loading Dose and Maintenance Dose.
- We were used the different polymers and exipients like sodium Bi- carbonate, so the drug is easily float and retarded in the GI fluid.
- The main objective of this strategy is that we get the proposed dissolution profile. (The tablet is dissolved in 24 hours till 95%).
- And the last requirement of this strategy we have to get the proposed dissolution profile.

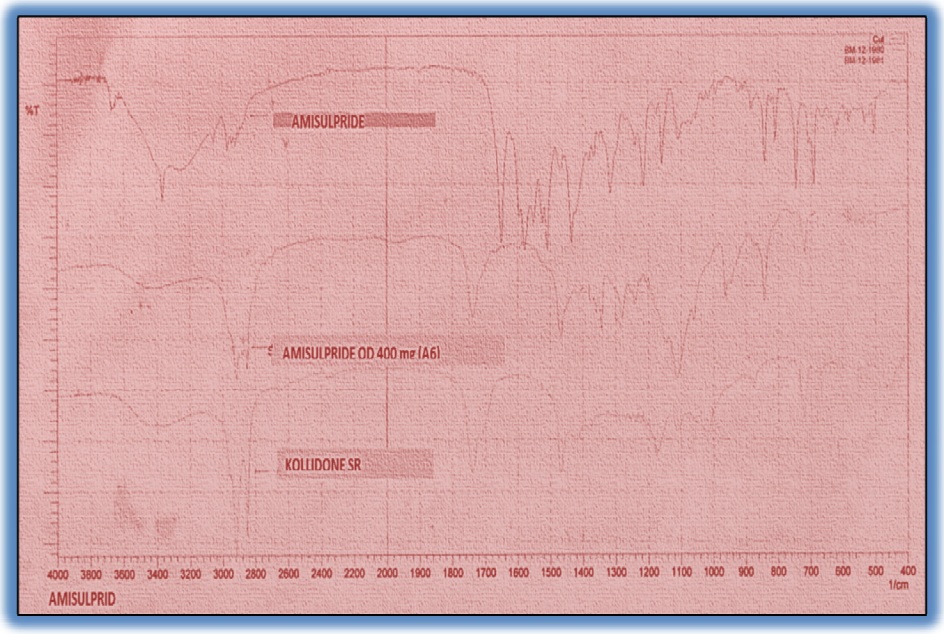

Figure 1: IR Spectra of Amisulpride standard, Amisulpride OD granules and Kollidone SR

Table 2:Formulation of the Amisulpride OD Tablets (400 mg) Quantities in per Tablets (AM1-AM6)

INGRERDIENTS	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
HPMC K 4M	--	95.00	95.00	100.26	100.26	100.26
Polyox	--	17.90	17.90	--	--	--
Carbopol 71G	--	--	20	20	20	20
Aerosil		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
$NAHCO_3$	--	-- --	--	--	--	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**	**560.00**	**990.00**	**990.00**	**999.00**

Table 3: Formulation of the Amisulpride OD Tablets (400 mg) Quantities in per Tablets (AM_7- |AM_{12})

INGRERDIENTS	AM7	AM8	AM9	AM10	AM11	AM12
Amisulpride	400	400	400	400	400	400
Polyvinyl Pyrollidine K-30	8.00	8.00	8.00	8.00	8.00	8.00
IPA	20%	20%	20%	20%	20%	20%
Water	20%	80%	80%	80%	80%	80%
Avesil	15.00	16.00	16.00	1600	15.00	15.00
HPMC K 4M	90.00	95.00	95.00	100.26	100.26	100.26
Polyox	--	17.90	17.90	--	--	--
Carbopol 71G	10	--	20	20	20	20
Aerosil		60	64	64	64	
Talc	19.75	25.75	19.75	19.75	19.75	19.75
Cross Carmelose Sodium	5.51	5.51	5.51	5.51	5.51	5.51
Starch	200.00	175.00	150.00	200.00	215.00	200.00
Kollidone SR	21.00	--	--	21.32	--	21.32
$NAHCO_3$	20.00	--	--	25.00	--	--
Xanthane Gum	---	3.50	3.50	.4.00	--	--
Mag.Stearate	4.50	1.50	1.50	3.50	4.50	4.50
Total	**980.00.00**	**920.00**	**910.00**	**990.00**	**920.00**	**990.00**

Table 4: Mean cumulative percentage release of Amisulpride OD Tablets(AM_1-AM_6) from (Inventive Product) in 0.01N HCL, pH 7.5 at 50 rpm USP type II apparatus.

MEDIA VOLUME: 900ML, APPRATUS: USP II

MEDIUM	TIME (hrs)	(BATCH NO: AM1 % drug dissolved 75 RPM (IR:SR=30: 70)	(BATCH NO: AM2 % drug dissolved 50 RPM (IR:SR=30: 70)	(BATCH NO: AM3(placebo) % drug dissolved 75 RPM IR+ SR mix (IR:SR=30: 70)	(BATCH NO: AM4 % drug dissolved 50 RPM (IR:SR=30: 70)	(BATCH NO: AM5 % drug dissolved 50 RPM (IR:SR=30: 70)	(BATCH NO: AM6 % drug dissolved 50 RPM (IR:SR=20: 80)
0.1N HCl	2	44	45	17	45	31	34
pH 3.0 Acetate Buffer	4	53	55	28	54	45	46
	6	59	60	38	59	52	53
	8	60	62	42	60	53	55
	10	64	66	45	61	57	57
pH 6.8 Phosphate Buffer	12	73	68	58	70	68	68
	14	75	69	62	72	71	70
	16	80	71	66	75	74	75
	18	83	73	72	78	77	78
	20	88	75	76	80	80	84
	22	90	77	80	84	82	90
	24	91	79	84	85	86	95
Remarks							RSD more

Table 5: Mean cumulative percentage release of Amisulpride OD Tablets(AM_7-AM_{12}) from (Inventive Product) in 0.01N HCL, pH 7.5 at 50 rpm USP type II apparatus

MEDIA VOLUME: 900ML, APPRATUS: USP II

MEDIUM	TIME (hrs)	(BATCH NO: AM7 % drug dissolved 50 RPM (IR:SR=20: 80)	(BATCH NO: AM8 % drug dissolved 50 RPM (IR:SR=30: 70)	(BATCH NO: AM9 % drug dissolved 50 RPM (IR:SR=30: 70)	(BATCH NO: AM10 % drug dissolved 50 RPM (IR:SR=20: 80)	(BATCH NO: AM11 % drug dissolved 50 RPM (IR:SR=20: 70)	(BATCH NO: AM12 % drug dissolved 50 RPM (IR:SR=20: 80)
0.1N HCl	2	44	45	45	51	44	43
pH 3.0 Acetate Buffer	4	46	55	49	53	47	46
	6	48	60	53	56	53	55
	8	51	62	55	59	54	59
	10	55	66	59	62	57	62
pH 6.8 Phosphate Buffer	12	62	71	62	67	60	68
	14	64	81	64	70	62	70
	16	68	82	66	73	66	74
	18	76	84	75	81	74	83
	20	78	85	79	83	76	86
	22	80	87	84	87	80	88
	24	92.0	89.0	88.0	93.0	85.0	90.0
Remarks							

***In-vitro* drug release of Amisulpride OD tablet in 0.1N HCL and phosphate buffer pH 6.8 :**

The % drug release of Amisulpride once daily tablet was plotted as a function of time. The percentage of drug release of formulations (Am1- Am12) varied from 17.00 % to 94.95% depending upon differences in the $NaHCO_3$ /Kollidone SR concentrations. Formulations Am6, Am7, Am10 show the highest drug release in 23 hrs

40 minute i.e. 94.95%, 92.00% and 93.13% respectively. The formulation Am6 prepared using moderate concentrations of $NaHCO_3$ /Kollidone SR due to which % drug release of (94.95.%) after 23 hrs 40 minute is achieved.

Hence formulation Am6 considered as the best one among the optimized formulations and studied for further characterizations.

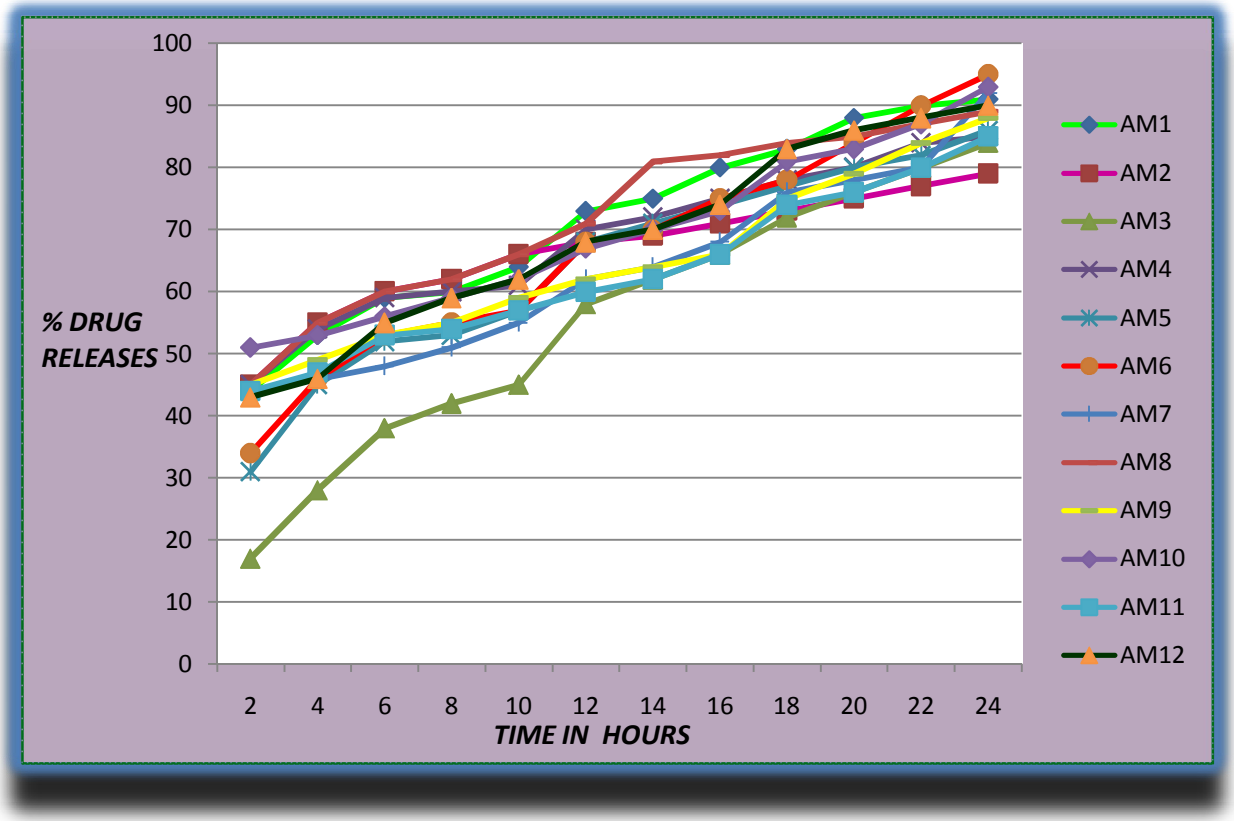

Figure 2: Mean cumulative percentage release of Amisulpride OD Tablets (AM_1-AM_{12})

SCANNING ELECTRON MICROSCOPY:

Scanning electron microphotographs of microspheres showing their shape and surface of Batch Am6 granules.

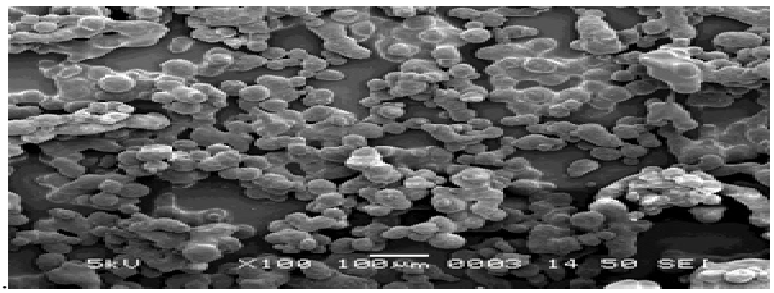

Figure 3: Scanning electron microscopy Amisulpride Am6 of the granules shape.

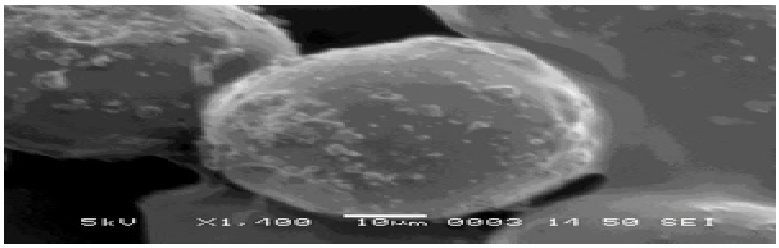

Figure 4: Scanning electron microscopy of the Amisulpride Am6 batch granules surface

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 Maintenancedose calculation. Micro Crystalline Cellulose (MCC) Ph 101 & Hydroxy Propyl Methyl Cellulose(HPMC) K4MCR were dispersed & sifted through #24 sieve. HPMC 3 Caps was dispensed & dissolvedin 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^o

C 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 through 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,AM_7,$AM_{10}$and AM_{12} 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 Amisulpride400mg tablets using $NaHCO_3$,Carbopol and Kollidone SR.

In compatibility study seems that a methyl group and hydroxyl methyl group of Kollidone SR are merging together and forming peak together.. In case of $NaHCO_3$ it was also not able to alter the position of peak I finger print region i.e 2000- 600 c.m-1. However due to the mixing of Amisulpride with $NaHCO_3$, some peaks becomes so weak. So that they are abolished. Otherwise the peak alteration have been observed at C-H stretch, aromatic stretch, methyl C-H stretch have been altered only by 2 cm-1 which is quietly significant. Thus we can conclude that the $NaHCO_3$ and Kollidone SR do not intercept the Amisulpride and thus is fully compatible with API i.e Amisulpride.

It was observed that the drug release from the formulations decreased with increase in amount of polymer added in each formulation. The release showed a biphasic release with an initial burst effect. In the first 2 hours drug release was 17.00% to 51.00 % for Am6 to Am12. The mechanism for the burst release can be attributed to the loading dose on IR part of the Amisulpride granules entrapment of the drug. The objective overall cumulative % release for Am6, Am7 and Am10 were found to be 95.00%, 92.00 % and 93.00 % at end of 24^{th} hr.AM_6 is best best fit formulation for objective because of highest time taken for dissolution.

The scanning electron micrographs of Amisulpride granules of the optimized batch Am6 were obtained using Jeol JSM-6380LV and the results obtained are shown in figure 3 and 4. The shapes of the granules were found to be spherical. The granules were showing smooth surface and the surface was not showing presence of drug crystals.

CONCLUSION:

The present investigation showed that the $NaHCO_3$ can be used to gastroretentive Amisulpride by bilayared tablet concept method. The effect of drug to polymer ratio was studied and forms the results, the following conclusions can be made:

- On the basis of *in vitro* release studies, Am_6 was selected as an optimized formulation for designing sustained release formulation. And for further study batch AM_6 were used for tableting.

- For the immediate release Amisulpride IR layer, it can be concluded that 4% of the Crospovidone (batch Am_2) showed maximum drug release, hence batch Am_2 was selected for IR batch further process.

- Studies on the directly compressible materials revealed that Kollidone SR was the best directly compressible material than MCC for compressing of Amisulpride SR Layer.

- The results of kinetic study showed that the compressed bilayared tablets followed first order kinetics and coupling gastro retention of dosage form by swelling mechanism so called gastroretentive mechanism.

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