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FORMULATION AND EVALUATION OF BREXPIPRAZOLE IMMEDIATE RELEASE TABLETS

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ABSTRACT

Objective: The aim and objectives of the present study is to develop a pharmaceutically stable, cost effective and quality improved formulation of Brexpiprazole immediate release tablets. **Materials and Methods:** The Brexpiprazole immediate release tablets are prepared by the wet granulation method, employing several polymer combinations, Brexpiprazole immediate release tablets were formulated by using microcrystalline cellulose (diluent), Sodium starch glycolate (super disintegrate), Povidone K 30 (binder) and magnesium stearate (lubricant) and Aerosil 200 pharma (carrier/glidant). Individual drugs and polymers and their physical mixtures were investigated by FTIR. Results: The formulation was subjected to pre-compression analysis such as bulk density, tapped density, compressibility index, Hausner's ratio, and angle of repose. After conducting in vitro drug release experiments, all of the formulations were assessed for pH, hardness, friability, drug content and weight variation test. **Conclusion:** Formulation F12 was considered the best formulation and immediate the release up to 88.9% at 1min 10 sec. Higher concentrations of SSG may work well as a carriers to increase drug release and produce a tablet with immediate release.

KEYWORDS: Brexpiprazole, Immediate Release, Schizophrenia, serotonin-dopamine activity modulator.

INTRODUCTION

Schizophrenia is a chronic and severe neuropsychiatric disorder characterized by symptoms such as hallucinations, delusions, disorganized thinking, and abnormal motor behavior. These symptoms not only cause significant emotional distress to affected individuals but also have profound social and familial impacts. If left untreated, schizophrenia can become persistent, leading to long-term disability and reduced quality of life.[1]

Brexpiprazole is an atypical antipsychotic and a novel D2 dopamine and serotonin 1A partial agonist called serotonin-dopamine activity modulator (SDAM). It has a high affinity for serotonin, dopamine and alpha (α)-adrenergic receptors.[8] Although it is structurally similar to aripiprazole, brexpiprazole has different binding affinities for dopamine and serotonin receptors. Compared to aripiprazole, brexpiprazole has less potential for partial agonist-mediated adverse effects such as extrapyramidal symptoms, which is attributed to lower intrinsic activity at the D2 receptor. It also displays stronger antagonism at the 5-HT1A and 5-HT2A receptors.[2,5,6]

Brexpiprazole was first approved by the FDA on July 10, 2015.[2] Currently approved for the treatment of depression, schizophrenia, and agitation associated with dementia due to Alzheimer's disease, brexpiprazole has also been investigated in other psychiatric disorders, such as post-traumatic stress disorder.[1]

Rapid-dissolving oral films (RDOFs) have emerged as an advanced drug delivery system designed to enhance solubility, improve patient compliance, and provide a faster onset of therapeutic action compared to conventional oral tablets. These films disintegrate quickly in the oral cavity without the need for water, releasing the drug for immediate absorption. Such dosage forms are especially beneficial for patients with swallowing difficulties, unconscious patients, or those requiring rapid therapeutic intervention**.** Drugs delivered via RDOFs may be absorbed **3–**10 times faster than conventional tablets, leading to improved bioavailability and faster clinical response.[7]

The present research focuses on the formulation and evaluation of Brexpiprazole rapid-dissolving oral films aimed at enhancing drug solubility, ensuring faster absorption, and ultimately improving therapeutic outcomes in the treatment of schizophrenia and depression.

MATERIALS AND METHODS

Materials: Brexpiprazole is obtained from a Nice laboratory, India. MCC is obtained from Divya Associates, Vijayawada, India. Analytical research grades of Sodium alginate and Povidine were obtained from SD Fine Chemicals and Sigma Aldrich, India, respectively. Every additional excipient was of analytical research quantity and was utilized exactly as supplied.

Pre-formulation study

Bulk density

The mass--volume ratio of an untapped powder sample is known as bulk density. In g/ml, the bulk density is expressed. Both the powder particle density and the powder particle arrangement affect the bulk density. The bulk density affects how the sample is prepared and stored. Below is the mathematical representation.

Bulk density = weight of the drug /bulk volume

Tapped density

When bulk powder is tapped for density, it is mechanically tapped in a graduated cylinder until a volume difference is noticed. Here, the tapped density is computed by dividing the mass by the powder's ultimate volume.

Tapped density = weight of the granules/ tapped volume

Angle of repose

It provides a sense of how easily granules or bulk solids can flow. The flowability of powders can be attributed to various factors, including the surface area, shape, and size of the particles. The powder's flowability varies with the environment and is easily adjustable. The following formula was used to get the angle of repose.

$$\theta = \tan^{-1} h/r$$

Where,

θ = angle of repose

h = height of the formed cone

r = radius of the circular base on the formed cone.

Carr's index

It is among the most crucial parameters for describing the granule's nature.

Carr's index (%) = (tapped density – bulk density / tapped density) x 100

Hausner's ratio

Determining the granule flow behavior in the presence of various polymer compositions is a crucial characteristic. This can be determined by the following formula:

Hausner's ratio = tapped density / bulk density

Good flow is indicated by values less than 1.25, and poor flow is indicated by values more than 1.25.

Post-compression study of formulated tablets

Weight variation test

Twenty tablets were picked randomly from each formulation and weighed separately using a digital balance (Shimadzu AUY 220, Uni Bloc, Germany). Mean values were calculated together with average weights. Approximately 5% deviation is the maximum allowed by the Indian Pharmacopeia (IP).

Tablet thickness test

Using Vernier callipers, the thickness of 20 randomly chosen tablets from each formulation is measured in order to assess the consistency and physical dimensions of the tablet.

Hardness test

The hardness of the tablets was measured using a Monsanto hardness tester. One of the key elements that plays a big part in transportation is hardness. Using a Pfizer hardness tester, the ten tablets hardness was determined. It is stated as kg/cm^2.

S.NO	INGREDIENTS	F1	F2	F3	F4	F5	F6
A. Dry mix Quantity (mg/tab)							
1.	Brexpiprazole	75.00	75.00	75.00	75.00	75.00	75.00
2.	Lactose monohydrate	131.20	179.00	195.00	189.00	195.00	175.00
3.	Microcrystalline Cellulose 101	54.80	-	-	-	-	-
4.	Aerosil 200	-	-	-	-	-	-

	pharma						
5.	Sodium Starch Glycollate	6.00	6.00	6.00	6.00	6.00	6.00
B.BINDER SOLUTION							
5.	Povidone K30	9.00	10.00	9.00	15.00	9.00	6.00
6.	Purified Water	q.s	q.s	q.s	q.s	q.s	q.s
C. BLENDING							
7.	Microcrystalline Cellulose 102	15.00	21.00	6.00	6.00	6.00	30.00
8.	Sodium Starch Glycollate	6.00	6.00	6.00	6.00	6.00	3.50
9.	Aerosil 200 pharma	1.50	1.50	1.50	1.50	1.50	3.00
D. LUBRICATION							
10.	Magnesium stearate	1.50	1.50	1.50	1.50	1.50	1.50
Average weight (mg)		300.00	300.00	300.00	300.00	300.00	300.00

S.NO	INGREDIENTS	F7	F8	F9	F10	F11	F12
A. Dry mix		Quantity (mg/tab)					
1.	Brexpiprazole	75.00	75.00	75.00	75.00	75.00	75.00
2.	Lactose monohydrate	174.00	175.00	190.00	150.00	150.00	150.00
3.	Microcrystalline Cellulose 101	-	-	-	45.00	45.00	45.00
4.	Aerosil 200 pharma	2.50	3.00	-	6.00	6.00	6.00
5.	Sodium Starch Glycollate	6.00	6.00	5.00	12.00	13.00	14.00
B.BINDER SOLUTION							
5.	Povidone K30	6.00	6.00	15.00	9.00	8.00	7.00
6.	Purified Water	q.s	q.s	q.s	q.s	q.s	q.s
C. BLENDING							
7.	Microcrystalline Cellulose 102	30.00	30.00	6.00	-	-	-
8.	Sodium Starch Glycollate	3.50	3.50	6.00	-	-	-
9.	Aerosil 200 pharma	1.50	1.50	1.50	-	-	-
D. LUBRICATION							
10.	Magnesium stearate	1.50	1.50	1.50	3.00	3.00	3.00
Average weight (mg)		300.00	300.00	300.00	300.00	300.00	300.00

RESULTS AND DISCUSSION

Table: Flow properties of blends of various trial batches.

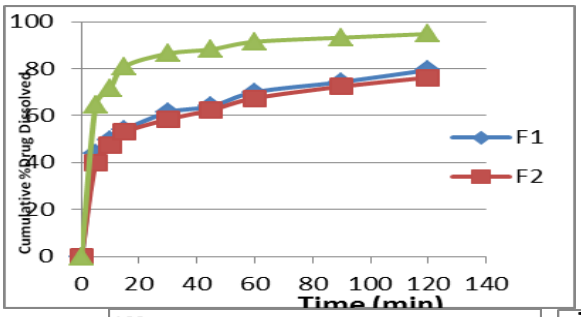
Formulation	Blend Property				
	B.D (gm/ml)	T.D (gm/ml)	C.I (%)	H.R	Angle of Repose
F1	0.50±0.013	0.63±0.061	20.97±2.445	1.26±0.028	45.91±2.05
F2	0.613±0.008	0.795±0.025	22.95±0.009	1.298±0.009	26.52±1.32
F3	0.65±0.003	0.75±0.165	9.56±0.009	1.18±0.165	29.56±1.64
F4	0.78±0.012	0.86±0.231	9.36±0.156	1.14±0.156	27.46±1.52
F5	0.72±0.011	0.79±0.013	9.25±1.447	1.10±0.018	28.41±1.69
F6	0.62±0.028	0.69±0.009	7.91±0.124	1.08±0.015	29.25±1.39
F7	0.68±0.009	0.74±0.011	8.20±0.098	1.89±0.001	28.54±0.42
F8	0.70±0.089	0.78±0.011	8.29±0.089	1.79±0.021	29.96±2.18
F9	0.62±0.015	0.67± 0.006	7.60±0.075	1.08±0.005	29.93±1.70
F10	0.544±0.014	0.697±0.018	22±0.224	1.282±0.011	26.47±0.70
F11	0.58±0.012	0.76±0.231	8.36±0.156	1.24±0.156	24.46±1.52
F12	0.574±0.015	0.635±0.015	20.513±0.226	1.248±0.014	26±0.014

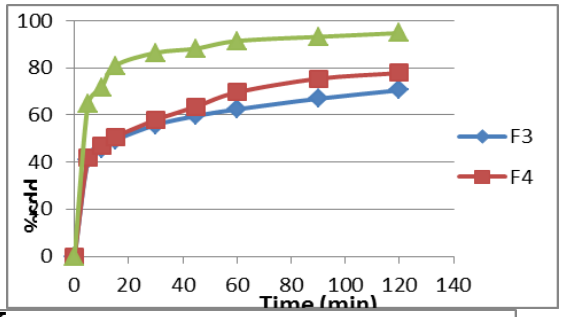
Table: Physical Evaluation of tablets of various trial batches.

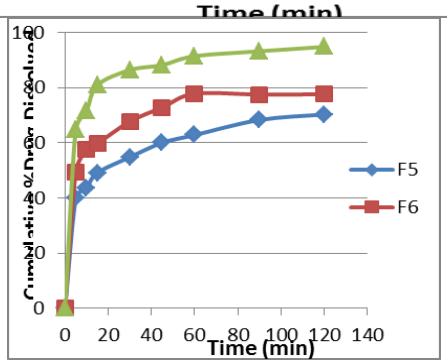
S. No	Physical paramete	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9	F 10	F 11	F 12
1	**Weight variation**	1.64	1.67	1.42	1.54	1.18	1.35	1.44	1.23	1.48	1.54	1.53	1.38
2	**Hardness (KP)**	8.8	8.4	8.2	9.55	9.23	8.8	9.4	7.8	8.5	8.8	9.0	8.6
	Thickness (mm)	4.41	4.50	4.50	4.37	4.47	4.85	4.89	4.80	4.93	5.12	4.12	4.14
4	**Friability %**	0.05	0.12	0.10	0.18	0.12	0.07	0.06	0.14	0.15	0.18	0.10	0.15
5	**Disintegration time**	3min 25sec	2min 30sec	2min 24sec	1min 29sec	1min 45sec	1min 20sec	1min 30sec	1min 40sec	1min 20sec	1min 18sec	1min 10sec	1min 10sec

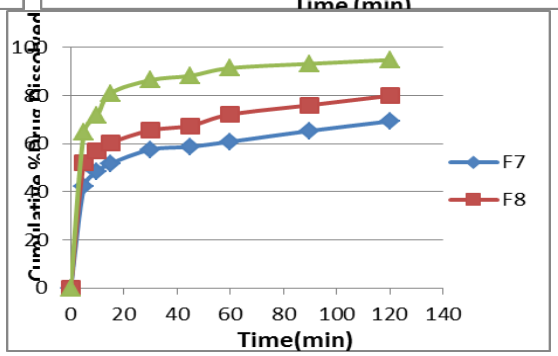
Table: Dissolution profile of brexpiprazole brand ir tablets (Rexulti).

Time (min)	Cumulative % drug dissolved	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0	0
5	64.6	44.0	40.1	40.8	41.8	39.8	49.2
10	71.6	49.5	47.5	45.6	47.1	43.7	57.6
15	80.9	53.9	53.0	49.3	50.7	49.1	59.7
30	86.4	61.4	58.4	55.8	57.9	54.8	67.7
45	88.2	63.9	62.4	59.6	63.6	60.0	72.8
60	91.4	70.0	67.4	62.4	69.6	62.8	77.8
90	93.2	74.3	72.4	66.9	75.4	68.3	77.5
120	94.8	79.4	76.2	70.5	77.8	70.3	77.6

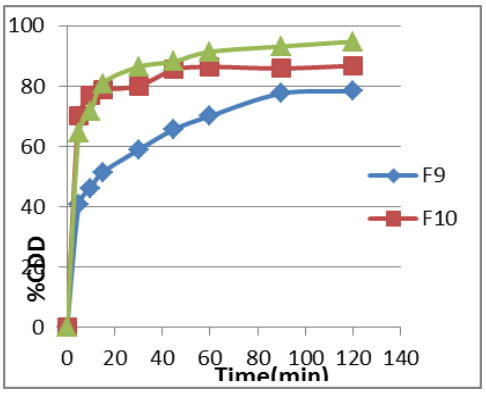


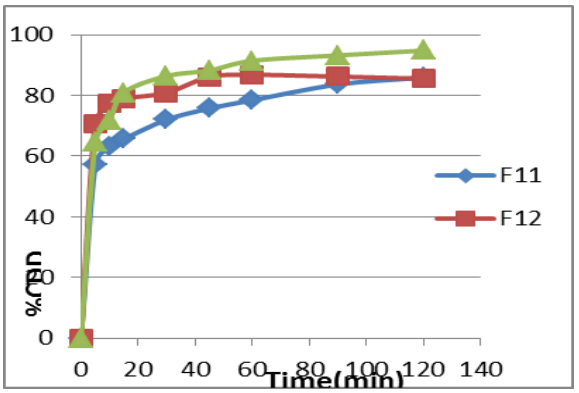






Time (min)	Cumulative %drug dissolved	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0
5	64.6	42.0	52.1	40.7	70.0	57.2	70.5
10	71.6	48.3	56.8	46.2	76.8	63.2	77.2
15	80.9	51.7	60.3	51.4	78.8	65.6	79.0
30	86.4	57.5	65.5	58.9	80.1	72.0	80.9
45	88.2	58.7	67.4	65.7	85.1	75.7	86.1
60	91.4	60.8	72.1	70.1	85.4	78.4	86.2
90	93.2	65.3	76.0	77.6	85.8	83.6	86.4
120	94.8	69.3	79.9	78.3	85.9	85.9	88.9





ACCELERATED STABILITY DATA

Comparative dissolution profile of F12 tablets after 15 Days stability with initial tablets.

Table: Dissolution data ofoptimized formulation after 15 days of optimized formulation after 15 days.

TIME	INITIAL	15 DAYS
0	0	0
5	70.5	65
10	77.2	73.5
15	79	77.8
30	80.9	79.2
45	86.1	84.6
60	86.8	85
90	86.2	84.7
120	85.5	84.4

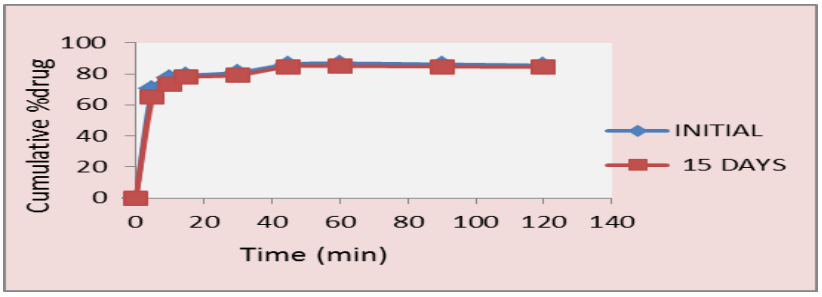


Figure: dissolution profile after 15 month stability.

TIME	INITIAL	1MONTH
0	0	0
5	70.5	62
10	77.2	72.5
15	79	77.8
30	80.9	79.2
45	86.1	84.6
60	86.8	85
90	86.2	84.7
120	85.5	84.4

Comparative dissolution profile after one month stability of F12.

TIME	INITIAL	1MONTH
0	0	0
5	70.5	62
10	77.2	72.5
15	79	77.8
30	80.9	79.2
45	86.1	84.6
60	86.8	85
90	86.2	84.7
120	85.5	84.4

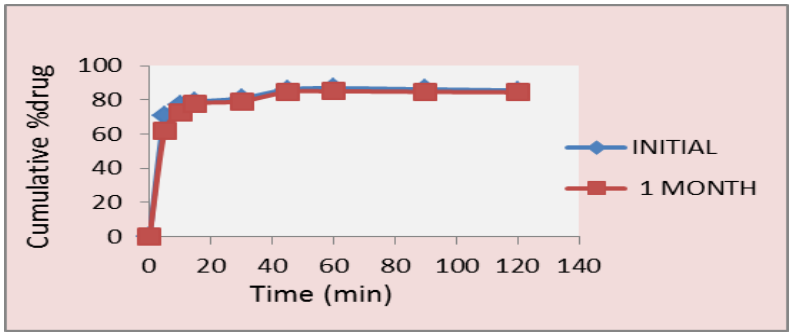


Figure: dissolution profile after 1 month stability.

Comparative dissolution profile after 2 month stability of F12

TIME	INITIAL	2MONTH
0	0	0
5	70.5	58
10	77.2	71.9
15	79	72.8
30	80.9	75.7
45	86.1	80.6
60	86.8	83
90	86.2	83.7
120	85.5	82.4

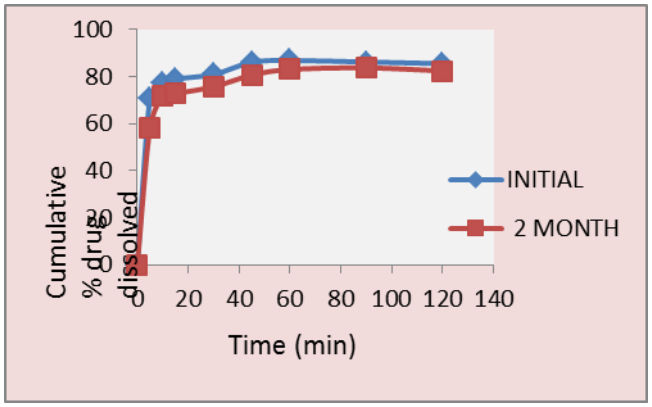


Figure: dissolution profile after 2 month stability.

CONCLUSION

Based on solubility data 0.1 N HCL was selected as the dissolution medium. Bulk density was found to be 0.321g/ml and CI was 55.07 % indicating that drug has to be granulated for the good flow properties. Melting point was found to be 257^0C indicating that drug has less sensitivity for drying temperatures. Drug – excipient compatibility studies indicate that the all excipients used in the formulation are compatible with the drug. RS (related substances) was found to be less than 0.5%. Among the 12 formulations prepared, formulation F12 was found to exhibit all the required properties. This is found to be pharmaceutically stable, once a day,

robust formulation. The physical attributes of the tablet were found to be satisfactory. Typical tablet defects such as capping, chipping and picking were not observed. The total weight of each formulation was maintained constant and the weight variation of the tablets was within limits of 5%. Hardness was found to be 8.6 KP. Friability was calculated as 0.15% which was within the acceptable range of 1% and indicated that tablet surfaces are strong enough to withstand mechanical shock or attrition during storage and transportation. Assay values were found to be within acceptable limits. The stability study for the selected formulation F12 was performed as per ICH guidelines. Stability study was carried out for 2 months at 40° C, 75%RH, according to ICH guidelines. The tablets were tested for drug release during the stability period and confirmed that results were found within the limits. The stability data reveals that the F12 showed a negligible change in drug content after storage in various conditions for two months according to ICH guidelines.

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CONFLICT OF INTEREST

There is no conflict of interest.

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