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Research Article

FORMULATION AND *IN-VITRO* EVALUATION OF LITHIUM CARBONATE EXTENDED RELEASE TABLET TO STUDY THE EFFECT OF VARIOUS CONCENTRATION OF HYDROPHILIC AND HYDROPHOBIC MATRIX IN COMPARISON WITH INNOVATOR'S PRODUCT

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ABSTRACT

Conventional lithium carbonate tablet produce rapid and relatively high peak serum lithium level which results in adverse effects. However, this limitation can be effectively overcome by extended release formulation. Innovator's lithium carbonate 300 mg extended release tablets produce an effective serum lithium concentration ranging between 1.0-1.5 mEq/L. The primary aim of the present study was to formulate an extended release tablet formulation of lithium carbonate using hydrophilic and hydrophobic matrix and to study the effect of various concentration of hydrophilic and hydrophobic matrix on *in-vitro* drug release of lithium carbonate from its extended release formulation in comparison with innovator's product. Eight formulations (F_1-F_8) were prepared by wet granulation method. Out of eight formulations, only formulation F_5 complies with USP limits at all time points and comparable with innovator's product. Hence the present study concludes that the *in-vitro* drug release profile of lithium carbonate extended release tablets prepared using Hydroxypropylmethyl cellulose K 4M was comparable with innovator's product at 5% w/w concentration.

Keywords: Bipolar Disorder, Extended Release Tablets, Hydroxypropylmethyl cellulose, Lithium Carbonate, Manic Depression

INTRODUCTION

About 51 million people worldwide, including 8.7 million people in India suffer from bipolar disorder which is also known as manic depression and it is the fifth leading cause of disability worldwide[1]. People with bipolar disorder will experience dramatic swing in mood, energy, frequent episodes of depression, and at least one incident of mania[2]. Till today, there is no complete cure for bipolar disorder, yet this long-term disorder can be cautiously managed throughout life with the help of medications such as mood stabilizers.

Lithium Carbonate (LC) was the first mood stabilizing agent approved by United States Food and Drug Administration for treatment and maintenance therapy of manic episodes[2]. Lithium has narrow therapeutic index in the range of 0.6-1.2 mEq/L. Patients may experience mild to moderate adverse reactions at concentrations between 1.5-2.5 mEq/L, and moderate to severe adverse reactions at concentrations between 2.0 mEq/L and above[3].

Conventional lithium carbonate tablet produce rapid and relatively high peak serum lithium level which results in adverse effects. However, this limitation can be effectively overcome by extended release formulation. Innovator's lithium carbonate 300 mg extended release tablets produce an effective serum lithium concentration ranging between 1.0-1.5 mEq/L[3-6].

The primary aim of the present study was to formulate an extended release tablet formulation of lithium carbonate using hydrophilic and hydrophobic matrix and to study the effect of various concentration of hydrophilic and hydrophobic matrix on the *in-vitro* drug release of lithium carbonate from its extended release formulation in comparison with Innovator's Product (IP).

MATERIAL AND METHODS

Materials

The following materials were used as received without any further purification. Lithium carbonate (Chemetall Foote Corporation, US), Hydroxypropylmethyl cellulose E 4M (Colorcon, India), Hydroxypropylmethyl cellulose K 4M (Colorcon, India), Carnauba wax (Koster Keunen Inc, US), Sodium starch glycollate (DFE Pharma, Germany), Povidone K 30 (BASF, India), Mannitol (Roquette, France), Talc (Luzinac, France), Magnesium stearate (Ferro Corporation, USA), Opadry pink (Colorcon, India), Concentrated Hydrochloric acid (Merck, India), Sodium acetate (Merck, India), Glacial acetic acid (Merck, India), Phosphoric acid (Merck, India), Potassium dihydrogen phosphate (Merck, India).

Drug-Excipient compatibility studies[10]

Compatibility between lithium carbonate and different excipients was studied by physical observation method. Briefly, lithium carbonate and each excipient were taken in the ratio of 5:1 and sieved to get uniform mixing. The mixtures were divided into two parts, first part was stored at 40°C and 75±5% RH for 4 weeks and second part was stored at 60°C for 2 weeks. Physical observations were made at initial and after 2nd week for the second part and after 4th week for the first part.

Preparation of Lithium Carbonate Extended Release Tablets

Eight formulations (Table 1) of lithium carbonate extended release tablets were prepared using hydrophilic and hydrophobic matrix by wet granulation method.

Briefly, lithium carbonate and sodium starch glycollate (SSG) were sifted through 60# mesh sieve along with release retardant such as Hydroxypropylmethyl cellulose E 4M (HPMC E 4M) or Hydroxypropylmethyl cellulose K 4M (HPMC K 4M) or Carnauba wax and mixed in rapid mixer granulator for 5 minutes at slow impeller speed. Povidone K30 was dissolved in purified water and transferred to the blend in rapid mixer granulator to get granulated wet mass which was then dried at 60±5°C using fluid bed drier. Drying was continued until the loss on drying (LOD) achieved less than 2.0% w/w. The dried granules were then sized by milling at medium speed. Mannitol, talc and magnesium stearate were then sifted and mixed with the sized granules using blender. Prepared granules were then tested for flow properties such as bulk density, tapped density and angle of repose as per the standard procedures.[10, 11] The resultant blend was compressed using 9.5 mm, circular, standard concave punches. The compressed tablets were then coated with opadry pink. Both uncoated and coated tablets were tested for hardness and thickness as per standard procedures.

In-vitro dissolution study

In-vitro dissolution study was carried out by using United States Pharmacopoeia (USP) 23 dissolution testing apparatus I (Basket method). The dissolution test was performed using 800 ml of dilute

HCl (7 in 1000) at 37±0.5°C at 100 rpm. At each time points (15, 45, 90, and 120 minutes), 8 ml of the solution was withdrawn and passed through a filter having a 35 µm or finer porosity. Filtrate was used to estimate the drug concentration.

Table 1: Formulations of extended release tablets of 300 mg lithium carbonate

Ingredients	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
Lithium carbonate (in mg)	300	300	300	300	300	300	300	300
HPMC E 4 M (in mg)	10	20	30	-	-	-	-	-
HPMC K 4 M (in mg)	-	-	-	10	20	30	-	-
Carnauba wax (in mg)	-	-	-	-	-	-	40	80
Povidone K 30 (in mg)	20	20	20	20	20	20	20	20
Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
SSG (in mg)	8	8	8	8	8	8	8	8
Mannitol (in mg)	47	37	27	47	37	27	17	7
Talc (in mg)	10	10	10	10	10	10	10	10
Magnesium stearate (in mg)	5	5	5	5	5	5	5	5
Uncoated tablet (in mg)	400	400	400	400	400	400	400	430
Opadry pink (3%)	12	12	12	12	12	12	12	12
Coated tablet (in mg)	412	412	412	412	412	412	412	442

RESULTS AND DISCUSSION

Drug-excipient compatibility study

Physical and chemical interaction between the drug and excipients in the formulation can significantly alter the physicochemical properties of either the drug or excipients or both which may raise the concern over the safety and efficacy of the formulation. Pharmaceutical quality by design (QbD) is a scientifically based proactive approach to pharmaceutical development, where the selection of excipients following compatibility investigation is the first step towards the final pharmaceutical formulation[7-9]. Hence, compatibility between lithium carbonate and different excipients was studied by physical observation method. Compatibility between lithium carbonate and different excipients was studied by physical observation method and the result (Table 2) demonstrates no significant incompatibilities between drug and excipients.

Preparation of Lithium Carbonate Extended Release Tablets

Lithium carbonate extended release tablets were prepared as per the formula in table 1. Prepared granules were then tested for flow properties such as bulk density, tapped density and angle of repose as per the standard procedures and found that the Hausner's ratio of granules was at or below 1.23 and angle of repose was at or below 1.23 which shows the good flow properties of granules. Results of characterization of granules are listed in table 3.

The compressed tablets were then coated with opadry pink. Both uncoated and coated tablets were tested for hardness and thickness as per standard procedures and found that the thickness of tablets were controlled within ± 5% variation and hardness of tablets was within the acceptable limit. Results of characterization of uncoated and coated tablets are listed in table 4.

In-vitro dissolution study

Percentage cumulative drug release of all 8 formulations of lithium carbonate extended release tablets was listed in table 5. Out of eight formulations, only formulation F_5 complies with USP limits at all time points and comparable with innovator's product. However, all other formulations (F_1 - F_4 and F_6 - F_8) do not compiles with USP limits at least in one time point which were shown in ***bolded italic*** in table 5.

Table 2: Summary of drug-excipient compatibility study

Samples (5:1 ratio)	Initial	2nd Week	4th Week
Lithium Carbonate	White-off white	White-off white	White-off white
LC + HPMC E4M	Off white	Off white	Off white
LC + HPMC K4M	Off white	Off white	Off white
LC + Carnauba Wax USP	Pale yellow	Pale yellow	Yellow mass
LC + Sodium Starch Glycollate	White-off white	White-off white	White-off white
LC + Povidone USP, K 30	White-off white	Pale yellow mass	Pale yellow mass
LC + Mannitol (SD 200)	White-off white	White-off white	White-off white
LC + Talc USP	White-off white	White-off white	White-off white
LC + Magnesium Stearate	White-off white	White-off white	White-off white
LC + Opadry Pink	Pink	Pink	Pink

Table 3: Summary of characterization of granules

Formulation	Granules Description	LOD (%w/w)	Bulk Density	Tapped Density	Hausner's Ratio	Angle of Repose
F_1	Off white	1.45	0.32	0.39	1.22	19°13"
F_2	Off white	1.63	0.34	0.41	1.21	18°98"
F_3	Off white	1.25	0.31	0.37	1.19	19°25"
F_4	Off white	1.32	0.34	0.40	1.18	19°03"
F_5	Off white	1.56	0.30	0.37	1.23	18°93"
F_6	Off white	1.51	0.35	0.43	1.23	19°33"
F_7	Pale yellow	1.76	0.33	0.40	1.21	20°21"
F_8	Pale yellow	1.82	0.32	0.38	1.19	19°87"

Table 4: Summary of characterization of coated and uncoated tablets

Batch	Granules description		Hardness (in N)		Thickness (in mm)	
	Uncoated	Coated	Uncoated	Coated	Uncoated	Coated
F_1	Off white	Pink Color	070-100	100 (080-120)	3.80±0.08	4.00±0.08
F_2	Off white	Pink Color	090-120	125 (110-140)	3.70±0.08	3.90±0.08
F_3	Off white	Pink Color	100-130	150 (130-170)	3.50±0.08	3.70±0.08
F_4	Off white	Pink Color	070-100	100 (080-120)	3.80±0.08	4.00±0.08
F_5	Off white	Pink Color	090-120	125 (110-140)	3.60±0.08	3.80±0.08
F_6	Off white	Pink Color	100-130	150 (130-170)	3.50±0.08	3.70±0.08
F_7	Pale yellow	Pink Color	070-090	125 (100-110)	4.00±0.08	4.20±0.08
F_8	Pale yellow	Pink Color	080-100	125 (100-120)	4.05±0.08	4.15±0.08

Table 5: Percentage cumulative drug release of F_1-F_8 Vs Innovator's Product

Formulation	Percentage cumulative drug release at				
	0 min	15 min	45 min	90 min	120 min
	USP limit				
	(0)	(2-16%)	(25-45%)	(60-85%)	(NLT 85%)
F_1	0.0	14.0±1.23	57.0±1.45	83.0±1.20	92.0±1.54
F_2	0.0	7.0±1.36	48.0±1.62	80.0±1.29	85.0±1.48
F_3	0.0	5.0±1.39	26.0±1.59	55.0±1.67	70.0±1.27
F_4	0.0	10.0±1.58	50.0±1.31	80.0±1.29	91.0±1.20
F_5	0.0	6.0±1.65	36.0±1.29	71.0±1.17	91.0±1.49
F_6	0.0	4.0±1.29	26.0±1.36	58.0±1.34	79.0±1.47
F_7	0.0	6.0±1.48	31.0±1.28	62.0±1.64	77.0±1.58
F_8	0.0	5.0±1.56	25.0±1.26	55.0±1.25	67.0±1.71
Innovator's Product	0.0	7.0±1.21	38.0±1.22	75.0±1.29	95.0±1.87

CONCLUSION

In the present study, formulations of lithium carbonate 300 mg extended release tablets were prepared with different concentrations of release controlling agents by wet granulation method. The *in-vitro* drug release profile of lithium carbonate extended release tablets prepared using Hydroxypropylmethyl cellulose K 4M was comparable with innovator's product at 5% w/w concentration.

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