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FORMULATION DEVELOPMENT AND CHARACTERIZATION OF LITHIUM CARBONATE EXTENDED RELEASE TABLET

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ABSTRACT

The favored and most patient convenient means of drug administration is oral route of drug delivery. Oral route is preferred over other non-oral route dosage forms mainly due to lower production cost, better appropriateness for self-medication, better patient compliance and a higher level of patient safety. Tablets and Capsules are most preferred and regularly used oral pharmaceutical dosage forms. The solid dosage forms can be designed into immediate release orextended release based on the drug physiological characteristics, dosage regimen, the condition to be treated and the patient's characteristics. In traditional drug delivery system, immediate release dosage form is required to be given repeatedly which might lead to the risk of dose variation, which rises the need of a formulation having extended release that maintain uniform level of drug in blood and that ultimately renders into improved patient compliance and boosted clinical effectiveness of the drug. 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. Conventional lithium carbonate tablet produces 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/L3. The primary aim of the present study was to formulate a 600 mg extended release tablet formulation of lithium carbonate using suitable polymer system.

INTRODUCTION

Extended release systems provide drug release in an amount sufficient to maintain the therapeutic drug level over an extended period of time, with the release profiles predominantly controlled by the special technological construction and design of the system itself. Development of oral extended release systems has been a challenge to formulation scientists due to their inability to restrain and localize the system at targeted areas of the gastrointestinal tract. There are numerous products in the market formulated for both oral and parenteral routes of administration that claim extended or controlled drug delivery. Extended release dosage forms release drug slowly, so that plasma concentration is maintained at therapeutic level for prolonged period of time. Lithium Carbonate was the first mood stabilizing agent for treatment and maintenance therapy of manic episodes. Lithium [8] 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. Conventional lithium carbonate tablet produces 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/L3.

2. MATERIAL AND METHOD

2.1 Material

Lithium Carbonate was received as a gift sample from the Microlabs Labs Ltd, Benglore, Karnataka, India. Other ingredients and solvents were obtained from different commercial suppliers.

2.2 Preformulation Studies

2.2.1 Drug-polymer compatibility study by FT-IR spectrophotometer

This was carried out to find out the compatibility between the drug and the polymer. About 1 mg of drug and 100 mg of KBr were taken in a mortar and triturated. A small amount of the triturated sample was taken into the DRS sample holder and scanned from 4000 cm^{-1} to 400 cm^{-1}at resolution of 4 cm^{-1} and 15 scans per spectrum.

2.2.2 Organoleptic properties

The colour and odour of Lithium carbonate was determined and reported by visual analysis.

2.2.3 Flow properties

Flow properties of material were determined by calculating parameters such as bulk density,
tapped density, compressibility index and hausners"s ratio and excipients for bulk density and
tapped density.

2.2.4 Angle of Repose

Angle of repose is determine by poured method. A funnel with a wide outlet is affixed at the distance of 10cm above yhe bench where a piece of paper is placed directly beneath the funnel. Powder is added while the funnel is closed. The contents flow through and collect on the paper. The diameter of cone and two opposite sides are measured with rulers.

$$\text{Angle of Repose} = \tan\theta = h/r$$

2.2.5 Bulk density and tapped density

10 g powder was placed in 100 ml measuring cylinder. Volume occupied by the powder wasnoted down as V, without disturbing the cylinder. Then cylinder was fitted in instrument andtapped for 500 times. Measure the difference between the initial volume and the final volume (after 500 taps). If the difference is more than 2%, then again tap the cylinder for 750 times more and measure the difference. Bulk density and tapped density was calculated using following formula:

$$\text{Bulk density (g/ml)} = \frac{\text{Weight of sample in grams}}{V0}$$

$$\text{Tapped density (g/ml)} = \frac{\text{Weight of sample in grams}}{Vb}$$

2.2.6 Hausner's ratio

It is the ratio of bulk volume to tapped volume or tapped density to bulk density.

$$\text{Hausner"s ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

2.2.7 Compressibility index

Tapped and apparent bulk density measurements can be used to estimate the compressibility
of the material

$$\text{Compressibility index} = 100 * \frac{(\text{Bulk volume} - \text{True volume})}{\text{Bulk volume}}$$

3. PREPARATION OF EXTENDED RELEASE LITHIUM CARBONATE TABLET

In the present study, the trials are taken to prepare extended release tablet of Lithium Carbonate. These are prepared by mixing the API with the base material in various weight proportions. At first we have to weigh API and all the excip[ients in the separate polythene bag. Sift sodium alginate, sodium starch glycolate, Hydroxyl propyl methyl cellulose (5 cps),Microcrystalline cellulose through 40 mesh. Sift yellow ferric oxide through 80 mesh and keep aside. Sift lithium carbonate through 40 mesh and keep aside. Load the material into rapid mixer granulator and mix for 5 minutes with impeller SLOW and chopper OFF.

In the next step, we are going for wet granulation. For preparation of binder, Dissolve Hydroxyl Propyl Methyl cellulose

(HPMC 5 cps) in purified water. Add binder solution into the mixed content. Mix the content for 3 minutes with impeller SLOW and Chopper OFF. stop the mixer scrap the sides and blades of the mixer. Mix further for the 60 to 120 seconds to get uniform distribution of binder and good granules with impeller FAST and Chopper Slow. A rough way to determine the end point is to pass a portion of wet mass in the palm of the hand. If the ball form crumbles under moderate pressure, the granules are formed and the mixture is ready for next stage. The mixing time required is generally 60 seconds to 120 seconds. If granules are not formed then add additional quantity of purified water for the formation of granules. Load the wet mass into FBD bowl and place the FBD in position. Start the blower and run for 10 minutes. Open the steam valve and adjust it to get the inlet temp of 60^0C to 65^0C. Fluidization air at low CFM and continue the drying for 5 minutes. Stop the blower motor and steam valve. Shake the finger bag with help of handle and take out the bowl. Scrap the side wall of the bowl and shuffle the granules in the bowl with the help of paddle. Continue drying until the LOD reached between 1.0% to 2.0%. Sift the dried granules of stage 06 through the sifter fitted with 20 mesh sieve. Collect the granules retained over 20 mesh sieve and mill through multimill at knives forward at medium speed with 1.5 mm screen and pass c dispensed quantity of Magnesium stearate and talc through 60 mesh sieve separately and add it into previous material and mix it for 5 minutes.

Compress the lubricated granules of with 16.5 X 8 mm capsule shape punch, plain on one side and breakline on other side.

4.0 Post Formulation Studies

4.1 Description

Colour and shape of the tablets were observed by visual observation.

4.2 Average weight of tablets

Twenty tablets were dedusted and weighed accurately.

4.3 Thickness

Ten tablets were randomly selected and thickness of the tablets was measured by previously calibrated vernier calliper.

4.4 Hardness test

Ten tablets were randomly selected. One tablet at a time was placed in the hardness tester which was already set at zero. Pressure was applied by pressing start button of the apparatus, till the tablet breaks. Reading on the tester, that is, hardness of tablets was noted down in newtons.

4.5 Friability test

Sample size of tablets corresponding to 6.5 gm was taken (recorded as weight X). These tablets were loaded to the friability test apparatus which was set to 25 rpm and after completion of 100 revolutions, tablets were removed, dedusted and weight of the tablet was noted down as Y.

$$\% \text{ friability} = \frac{X-Y}{X} \times 100$$

4.6 Uniformity of weight

20 tablets were randomly selected, dedusted and weighed individually. % weight variation from actual average weight of tablet was calculated using following formula.

$$\% \text{ weight variation from actual average weight of tablet} = \frac{100 \times (\text{Individual tablet weight} - \text{Average weight})}{\text{Average weight of tablet}}$$

4.7 Dissolution profile (IP method)

Dissolution testing for the amount of Lithium Carbonate with different polymers and varied Concentrations were studied using the following dissolution parameters:

Standard solution

Weigh accurately 20 mg of Lithium Carbonate and transfer to 100 mL volumetric flask. Add 75 mL of diluent, sonicate to disolve it completely, make the volume up to the mark with diluent. (200 PPM of Lithium Carbonate)Further dilute 2 ml of stock solution to 20 ml with diluent. (20 PPM of Lithium Carbonate)

Test Sample Preparation

Transfer 800 mL of Dissolution media in dissolution bowl previously maintained at 37°C. Attached apparatus 1 (Basket) and set at 100 RPM. Transfer one tablet in each bowl maintained at 37°C and subject for dissolution. Run the Dissolution program for 120 minutes(USP-NF). Withdraw the 10 mL of aliquot at the time point of 15, 45, 90 and 120 minutes (USP-NF) and replace with 10

mL of dissolution media. Filter the solution through suitable 0.45 µ PVDF syring filter discarding 3-5 mL of filtrate. Further dilute 1.3 ml of filtrate to 50 ml with diluent. (19.50 PPM of Lithium Carbonate) and % Lithium Carbonate released was calculated by estimating drug in dissolution medium using flame photometer.

4.8Stability study

The study consists of selected formulations of Extended releast Lithium Carbonate Tablet were kept in environmental stability chamber maintained at 40 ºC ± 2 ºC/75% ± 5%RH for six months and samples were analyzed as duration of Initial, 1, 3 and 6 months respectively for assay by using HPLC method.

Table No. 01: Pre-compression Parameters

Parameters	Specifications
Appearance	Yellow mottled, Capsule shape biconvex tablets plain on one side and breakline on other side
Average weight of compressed tablets (mg)	762 ± 3%
Group weight of 20 compressed tablets (gm)	15.24 ± 3%
Uniformity of weight (mg)	± 5% of target weight
Length (mm)	16.5
Width (mm)	8.0
Thickness (mm)	5.6 to 5.88
Friability (%)	NMT 1.0% W/W
Hardness (N)	140 to 160

Table no.2:Formulation of Extended Release Lithium Carbonate Tablet

Sr. No.	Content	Trial-1	Trial-2	Trial-3	Trial-4	Trial-5	Trial-6	Trial-7	Trial-8	Trial-9
1	Lithium carbonate	600.00	600.00	600.00	600.00	600.00	600.00	600.00	600.00	600.00
2	Sodium alginate	53.34	53.34	53.34	64.77	64.77	64.77	80.01	80.01	80.01
3	MCC	45.29	30.05	14.81	33.86	18.62	3.38	18.62	3.38	6.14
4	SSG	15.24	22.86	30.48	15.24	22.86	30.48	15.24	22.86	30.48
5	Ferric oxide yellow	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13
6	HPMC	26.67	34.29	41.91	26.67	34.29	41.91	26.67	34.29	41.91
7	Talc	13.33	13.33	13.33	13.33	13.33	13.33	13.33	13.33	13.33
8	Mg stearate	8	8	8	8	8	8	8	8	8
Total Weight of Tablet		762.00	762.00	762.00	762.00	762.00	762.00	762.00	762.00	762.00

Table No. 3 Photometric Parameters:

Diluent:	7 ml of HCl in 1000 mL of Distillted water.
Rinsing Solvent:	Distillted water
Instrument:	Flame Photometer
Filter:	Lithium filter
Mode	Emission Mode

5.0 RESULTS AND DISCUSSIONS

5.1 Pre-formulation Studies

5.1.1Drug-polymer compatibility study by FT-IR spectrophotometer

FT-IR spectroscopy study was carried out separately to check the compatibility of the drug and polymer used for the preparation of Extended Release Tablet. FT-IR was performed for the drug, polymer and physical mixture of drug and polymer. The spectrum obtained from FT-IR spectroscopy studies at wavelength from 4000 cm^{-1} to 400 cm^{-1} are

shown in figure 1, 2 and 3 and the characteristic peaks obtained are shown in table 1, 2 and 3.

5.1.2Organoleptic properties

Lithium Carbonate is white powder having characteristic odour.

5.1.3Angle of Repose

Angle of repose is determining by poured method. It is performed for all the formulation batches. Values are given in table no7.

5.1.4Bulk density and tapped density

10 g powder was placed in 100 ml measuring cylinder. Volume occupied by the powder was noted down as V, without disturbing the cylinder. Then cylinder was fitted in instrument andtapped for 500 times. Now measure the difference between the initial volume and the final volume (after 500 taps). If the difference is more than 2%, then again tap the cylinder for 750 times more and measure the difference.All the results shows appreciable values which are given in table no 7.

5.1.5Hausner's ratio

It is the ratio of bulk volume to tapped volume or tapped density to bulk density. Hausner"s ratio is indicative of the flow properties of the material. A value less than 1.25 is indicative of good flow and more than 1.25 indicates poor flow. Final values are given in table no 7.

5.1.6Compressibility index or Carr's index

Compressibility index is indicative of the flow properties of the material. An index of below 15 indicates good flow properties while an index of greater than 25 is indicative of poor flow of the material. . Final values are given in table no 7.

5.2Post-Formulation

5.2.1 Description of Prepared Tablet

Tablet is Yellow mottled, Capsule shape biconvex tablets plain on one side and breakline on other side

5.2.2 Average weight of tablets

Twenty tablets were dedusted and weighed accurately. Which are observed as 15.24 gm ± 3%.

5.2.3 Hardness

Ten tablets were randomly selected. One tablet at a time was placed in the hardness tester which was already set at zero. Pressure was applied by pressing start button of the apparatus, till the tablet breaks. Reading on the tester, that is, hardness of tablets was noted down in newtons. Results are noted down in the table no 8.

Acceptance criteria: The tablet passes the test if it falls in the range of 140-180 N. The lowest hardness at which the tablets pass the friability test was used to decide the hardness range.

5.2.4 Friability test

Sample size of tablets corresponding to 6.5 gm was taken (recorded as weight X). These tablets were loaded to the friability test apparatus which was set to 25 rpm and after completion of 100 revolutions, tablets were removed, dedusted and weight of the tablet taken. Results are noted down in the table no 8.

Acceptance criteria: Friability of tablets should be less than 1% as per USP

5.2.5 Uniformity of weight

20 tablets were randomly selected, dedusted and weighed individually. % weight variation from actual average weight of tablet was calculated. Results are noted down in the table no ……..

Acceptance criteria: The tablet passes the test if not more than two tablets are outside the percentage limit and if no tablet differs by more than two times the percentage limit. Thefollowing percentage deviation in weight variation is allowed.

5.2.6 Thickness

Ten tablets were randomly selected and thickness of the tablets was measured by previously calibrated vernier calliper. Results are noted down in the table no 8.

Acceptance Criteria: 5.6± 0.3 mm for LC ER Tablet

5.2.7 Dissolution Profile:

The dissolution studies carried out by using USP Type I (Basket Type) apparatus. In that study, the samples withdrawal in the interval of 15, 45, 90 and 120 minutes(USP-NF) and % dissolution study carried out by using flame photometry. In that study, batch no. F1 to F7 shows appreciable results from which batch no. F5 shows maximum dissolution while Batch No. F8 and F9 shows results bellow 80%. Results are shown in table no. 09.

6.0 Stability study

The results of effect of temperature and humidity at 40 ºC ± 2 ºC/75% ± 5%RH for 6 months in environmental stability chamber on selected formulation are shown in table. There was no significant change in assay of LC tablet, the samples analyzed after 1, 3 and 6 months of storage & there was no significant change in percent assay after 6 months. Hence, from the below results, it can be concluded that the developed formulations were stable and retained their pharmaceutical properties over a period of 6 months. Results are shown in following table no.10

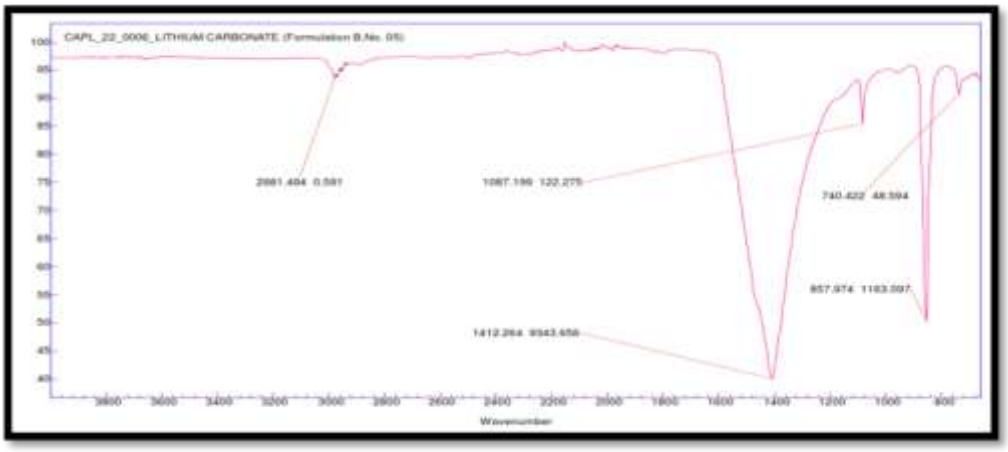

Fig no 1: IR Spectra of Lithium Carbonate

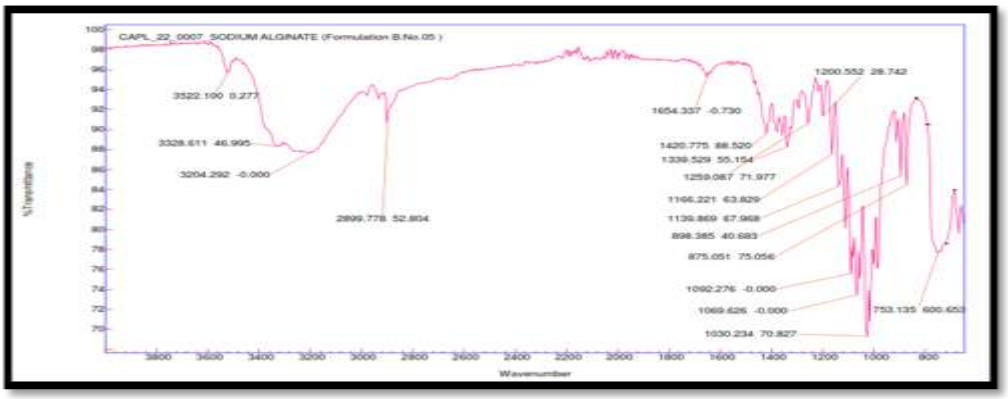

Fig no 2: IR Spectra of Sodium Alginate

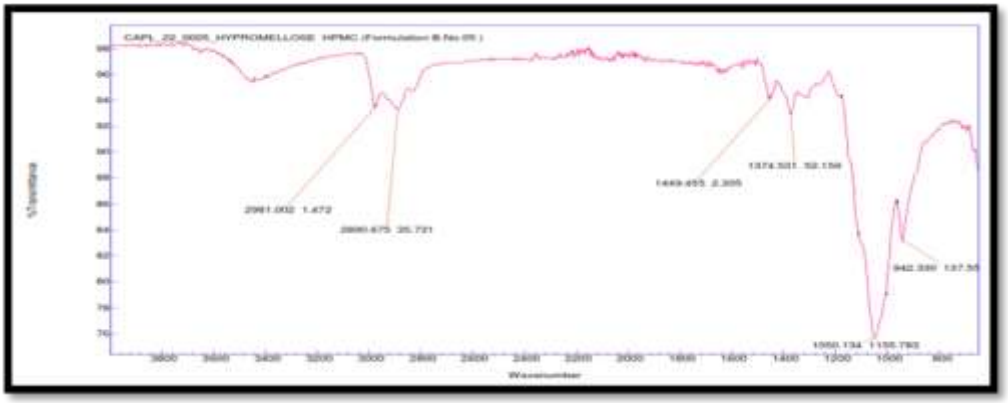

Fig no 3: IR Spectra of HPMC

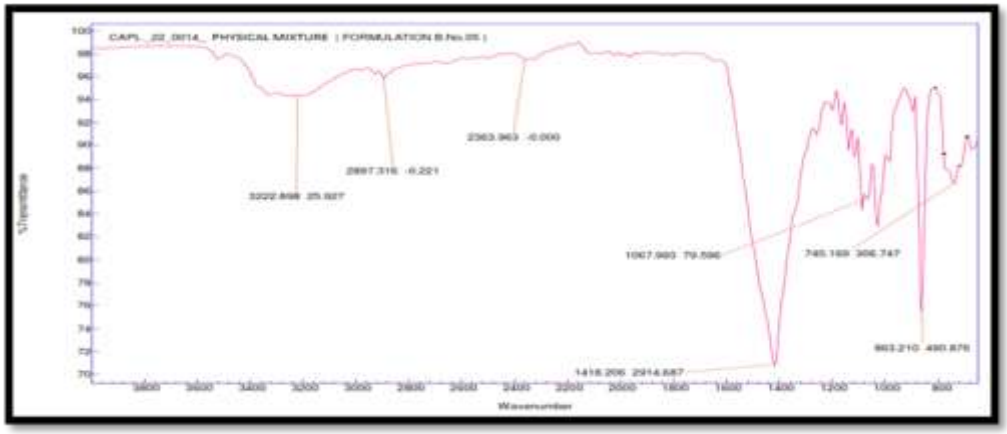

Fig no 4: IR Spectra of Physical mixture

Table No 4: IR interpretation of Lithium Carbonate

Obtained peak value (cm^{-1})	Standard ranges of wave number (cm^{-1})	Bond	Characteristic functional group
2981.49	3300-2500	C=O(Bending)	Esters, Carboxylic Acids
1412.26	1440-1395	O - H (Bending)	Alcohol, Esters
1087.19	1090-1050	C-O (Stretching)	Primary Alcohol
857.97	900-700	C - H(Stretching)	Alkane, Tri-substitutes
740.42	775-735	C - H (Bending)	Tri-substituted

Table No 5: IR interpretation of Sodium Alginate

Obtained peak value (cm^{-1})	Standard ranges of wave number (cm^{-1})	Bond	Characteristic functional group
3522.100	3200-3550	O-H(stretching)	Alcohols
3204.29	3200-3550	H - O(Broad)	Alcohols, esters, carboxylic acid
1654.33	1658-1648	C –H (Medium)	Alkane
1030.23	800-1200	C-C(Streching)	Aromatic
930.11	950-910	O - H (Bending)	Alcohol
898.38	898-855	C = C(strong)	Alkenes
753.13	735-775	C – H (Bending)	Disubstituted

Table No6: IR interpretation of Physical mixture

Obtained peak value (cm^{-1})	Standard ranges of wave number (cm^{-1})	Bond	Characteristic functional group
3222.100	3200-3550	O-H(stretching)	Alcohols
3204.29	3200-3550	H = O(Broad)	Alcohols, esters, carboxylic acid
2897.31	3000-2840	C-H (Bending)	Methylene Group
1654.33	1658-1648	C –H (Medium)	Alkane
1418.20	1440-1395	O - H (Bending)	Alcohol, Esters
1030.23	800-1200	C-C(Streching)	Aromatic
863.21	898-855	C = C(strong)	Alkenes
740.16	735-775	C – H (Bending)	Disubstituted

Table No. 7 Preformulation Parameters

Formulation code	Angle of repose	Bulk density (g/cm3)	Tapped density (g/cm3)	Hausner's ratio	Compressibility index (%)
F1	32.67º	0.833	0.909	1.09	8.36
F2	31.82º	0.869	1.001	1.15	13.1
F3	32.41º	0.869	0.952	1.09	8.31
F4	29.35º	0.714	0.821	1.12	10.75
F5	28.34º	0.701	0.805	0.998	12.3
F6	31.86º	0.895	0.905	1.13	9.88
F7	29.48º	0.813	0.852	1.15	10.18
F8	30.96º	0.855	0.921	1.02	9.26
F9	31.25º	0.89	0.859	1.19	9.92

Table No. 8 Post Formulation Parameters

Formulation code	Hardness N	Friability (%)	Weight variation (mg)	Thickness (mm)
F1	145	0.15	761.5± 5%	5.6± 0.3
F2	165	0.16	760.8± 5%	5.6± 0.3
F3	165	0.18	763.8± 5%	5.7± 0.3
F4	170	0.15	760.9± 5%	5.7± 0.3
F5	168	0.15	763.7± 5%	5.6± 0.3
F6	175	0.16	759.7± 5%	5.7± 0.3
F7	162	0.17	764.8± 5%	5.6± 0.3
F8	155	0.19	760.2± 5%	5.7± 0.3
F9	168	0.2	758.5± 5%	5.6± 0.3

Table No. 9: Dissolution Profile

Batch No	Time in Minutes			
	15 Min.	45 Min.	90 Min.	120 Min.
	% Dissolution			
F1	27.3	58.6	92.4	93.6
F2	22.6	59.2	94.1	97
F3	21.6	54.8	88.9	89.8
F4	20.2	48.4	85.9	87.4
F5	13.8	38	78.3	93.1
F6	5.7	27.4	57.6	83.6
F7	5.1	27.4	54.9	82.3
F8	4.7	23	56.5	77.2
F9	5.1	22.6	52.8	76.6

Table No. 10. Stability Study

Time point	% Assay	% Absolute difference from initial assay value	Acceptance criteria
Initial	98.43	NA	**% Absolute difference from initial assay: NMT 5.0**
1 Month	97.94	0.50	
3 Month	97.38	1.07	
6 month	95.59	2.89	

7. CONCLUSION

In the present study, attempts were made to study the properties of Lithium Carbonate Extended Release tablet. In that study the trial no. F5 for LC ER tablet shows maximum good results. The possible drug and polymer interaction during the time of preparation was studied using FT-IR analysis. The result of FT-IR study revealed that there was no interaction between the selected drug and polymer. The pre-formulation parameters like angle of repose, bulk density, tapped density, Hausner's Ratio and Compressibility index were studied which shows appreciable results. In formulation of Lithium Carbonate Extended Carbonate Tablet, total 9 batches conducted by following 3^2 factorial design and amont that batch no F5 shows appreciable results. Post formulation characteristics like hardness of tablet, friability, average weight of tablet and content uniformity also conducted and they shows better results.The dissolution study were also done for all 9 batches and found to be having good dissolution characteristics for batch no 5. All the results are follows USP standards. The final formulation was studied for effect of temperature and humidity in stability chamber for 6 months. The studies indicated that the formulations were stable and retained their pharmaceutical properties over period of 6 months.

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