Research Article

Formulation and evaluation of sustained release matrix tablet of lithium carbonate using hydroxypropyl methylcellulose

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ABSTRACT

Aim: The aim of the study was to prepare matrix tablet of lithium carbonate using hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) (used in different ratio) and Eudragit S 100 to obtain sustained release characteristics to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose and producing a desirable blood serum level which, in turn, lead to a decrease in the occurrence of drug toxicity. **Methodology:** The tablets were prepared by wet granulation method using different polymers such as HPMC (as release retardant), Eudragit S 100, Crospovidone, and Gum acacia in different combinations as F1 to F5. The prepared formulations were evaluated for hardness, thickness, weight variation test, content uniformity, friability, swelling index, and subjected to *in vitro* drug release studies. Swelling index was reported to increase with the time duration. **Results:** All the formulations showed acceptable pre- and post-compression properties. Swelling behavior of sustained release matrix tablets showed increase in percent weight gain in phosphate buffer pH 6.8 due to increase in amount of hydrophilic polymer. The results obtained revealed that HPMC at a concentration of 30% in formulation F4 was able to sustain the drug release for 12–14 h. **Conclusion:** Hence, combinely HPMC and Eudragit at suitable concentration can effectively be used to sustain the drug release.

Keywords: Hydroxypropyl methylcellulose, lithium carbonate, sustained release matrix formulation

Introduction

During the last two decades, there has been remarkable increase-e in interest in the sustained release drug delivery system. This has been due to various factors, namely, the prohibitive cost of developing new drug entities, expiration of existing international patents, discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems. These systems also provide a slow release of drug over an extended period of time and also are successful at maintaining constant drug levels in the target tissue or cells. It is, particularly, suitable for the drugs with narrow therapeutic index which may produce adverse effects at therapeutic concentration on repeated administration.

One of such drug candidates is lithium which is the simplest therapeutic agent for the treatment of depression and has been used for over 100 years. Lithium carbonate and some other lithium salts are used for the treatment of some psychiatric illnesses, particularly, bipolar mood disorders. Lithium carbonate induces a wide range of intra- and extra-cellular changes and most emphasis has been naturally on the similarities with $Na^+/K^+/Ca^{2+}/Mg^{2+}$ ions.[1-3] It is presumed that lithium alters the transport of sodium ions in neurons, thus influencing the intercellular contents of catecholamines, normalizing the mental state, and not causing general lethargy. It is used for mania conditions of various origins, preventative measures, and for treating affective psychoses.[4]

Conventional tablets of the lithium carbonate make the drug immediately available for absorption producing rapid and relatively

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high peak blood levels resulting in adverse effects associated with high or even at therapeutic serum concentrations achieved on repeated administration.[4] These drawbacks can be overcome by designing suitable sustained release formulations of the same. Lithium carbonate (LC) with half-life of 20–24 h and narrow therapeutic index (4.2–8.3 mg/L) is widely used for the prophylaxis and the treatment of manic depression and mania and in the maintenance treatment of recurrent depression.[5] As discussed earlier, the drug has narrow therapeutic index and many of the side effects of lithium are dose related.[6,7] Initial adverse effects of lithium therapy include nausea, diarrhea, vertigo, polyuria with polydipsia, and muscle weakness.[8] Those effects occurring at therapeutic serum concentrations include anorexia, constipation or diarrhea, epigastric discomfort, headache, and vertigo.

This can be overcome by formulating a suitable sustained release formulation of the lithium salts. Matrix tablet is one of the most widely used approaches to sustain the drug release. It involves the manufacture of sustained release dosage forms by direct compression of blend of drug, retardant material, and the additives to formulate a tablet in which the drug is embedded in a matrix of the retardant.[6,9,10] The materials most widely used in preparing matrix systems includes both hydrophilic and hydrophobic polymers.[11-14] Commonly available hydrophilic polymers include hydroxypropyl methylcellulose (HPMC), hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), Xanthan gum, Sodium alginate, Poly (ethylene oxide), and crosslinked homopolymers and copolymers of acrylic acid.

Thus, incorporation of lithium salts within matrices containing a suitable polymer which can provide a sustained release formulation, capable of controlling the release rate of the drug over an extended period of time and producing a desirable blood serum level which, in turn, lead to a decrease in the occurrence of drug toxicity.

The present study aims at developing sustained release dosage form of lithium carbonate with an extended release pattern, using hydrophilic HPMC, Eudragit S 100, Crospovidone, and Gum acacia as retarding polymers. Various formulations were prepared, and physicochemical characterization was carried out. Further the appropriate formulations were selected, and the dissolution behavior and release kinetics of the tablets were evaluated.

Materials and Methods

Lithium carbonate was obtained from Research lab, Mumbai. Other samples such as HPMC were purchased from Rajesh Chemicals, Sholapur, and Eudragit S 100, Crospovidone, magnesium stearate and Alginic acid were obtained from Research lab, Mumbai. Furthermore, Gum acacia and Aerosil were purchased from SD Fine Chemicals, Mumbai. All other reagents, chemicals, and solvents used were of analytical grade.

Pre-formulation studies

Characterization of pure lithium carbonate drug:
The physiochemical characterization of drug molecules is important in design and development of formulations. Melting point of the drug and its solubility in different solvents was determined. The ultraviolet absorption spectrum of solution of lithium carbonate in phosphate-buffered obtained using Shimadzu 1800 UV spectrophotometer and 1 cm quartz cell scan over a wavelength range of 200–400 nm. The infrared (IR) spectra of the pure drug and HPMC were obtained.

Method development and validation by UV spectroscopy

Preparation of standard curve of lithium carbonate was carried out using phosphate-buffered pH 6.8 using different dilutions of the stock solution containing 1000 µg/ml.

Formulation of lithium carbonate matrix tablets

The tablet batches were prepared by wet granulation method. The composition of different formulations of lithium carbonate sustained release matrix tablets is shown in Table 1. The ingredients, lithium carbonate, i.e., API and HPMC, were weighed accurately and mixed thoroughly then were granulated with an ethanolic solution of Eudragit S 100. Granules were passed through mesh no. 18 and dried at 45°C for 2 h. The dried granules were mixed with other formulation components and then compressed into the tablet.

Evaluation of pre-compression properties/ powder blend

Pre-compression properties of the blend such as angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio were determined.

1. Angle of repose: A funnel with 10 mm diameter of stem was fixed at a height of 2 cm, over the platform. Sample was slowly passed along the wall of the funnel till the tip of pile formed touches the stem of the funnel. A rough circle was drawn around pile base and the radius of powder cone was measured.

Angle of repose was calculated from the average radius using formula:

$$\emptyset = \tan^{-1}(h/r)$$

Table 1: Composition of matrix tablet of lithium carbonate

Ingredients (mg)	Formulation code				
	F1	F2	F3	F4	F5
Lithium carbonate	450	450	450	450	450
Pure HPMC	10	15	25	30	35
Eudragit S 100	15.5	15.5	15.5	15.5	15.5
Crospovidone	0.75	0.75	0.75	0.75	0.75
Gum acacia	70	65	55	50	45
Aerosil	0.33	0.33	0.33	0.33	0.33
Magnesium stearate	3.3	3.3	3.3	3.3	3.3
Iron oxide	0.5	0.5	0.5	0.5	0.5
Alginic acid	0.5	0.5	0.5	0.5	0.5
Total weight (mg)	550	550	550	550	550

Where,

Ø = Angle of repose

h = height of the pile

r = average radius of the powder cone

2. Bulk density (BD): Bulk density was determined by pouring sample through glass Funnel into 100 ml graduated cylinder. The volume occupied by the sample was recorded. Bulk density was calculated.
3. Tapped density (TD): It was determined by pouring sample through a glass funnel into a 100 ml graduated cylinder. The cylinder was tapped from height of 2 in Suntil a constant volume was obtained. Volume occupied by the sample after tapping was recorded and tapped density was calculated.

Tapped density = weight of sample/volume occupied by the sample

4. Compressibility index: In recent years, the compressibility index and the closely related Hausner's ratio have become the simple, fast, and popular method of predicting powder flow characteristics. The compressibility index and Hausner's ratio are determined by measuring the bulk density and tapped density of powder.

The flow ability of powder can be evaluated by comparing the bulk density and tapped density of powder and the rate at which it packed down.

Compressibility index is calculated by

Compressibility index (%) = TD-BD/ TD ×100

5. *Hausner's ratio: It is the ratio of tapped density to bulk density.

Hausner's ratio = TD/BD

Evaluation of the prepared formulation for physicochemical characteristics/tablet

Each tablet formulation was monitored for thickness, hardness, weight variation, friability, drug content, and swelling index.[6,15,16-19]

1. Tablet Dimensions/Thickness: Thickness and diameter were measured using a calibrated Vernier caliper. Five tablets of each formulation were picked randomly, and thickness was measured individually.
2. Hardness: Hardness of tablet was measured using digital hardness tester. It is the pressure required to fracture diametrically placed tablets by applying the force. The hardness of five tablets from each atch was determined and average of reading in triplicate was calculated, which was expressed in kg/cm².
3. Weight Variation Test: Tablets are weighed individually, calculated the average weight and compared the individual tablet weight to the average IP weight variation test.
4. Friability: Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap, or break. The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). Twenty tablets were initially weighed (Winitial) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions. The tablets were weighed again (Wfinal). % Friability of tablets <1% was considered acceptable. The % friability was then calculated.

$$\%F = (1-W_0/W) \times 100$$

Where,

%F = friability in percentage

W_0 = initial weight of tablet

W = weight of tablets after revolution.

5. Uniformity of drug content: Five tablets of each type of formulation were weighted and crushed in mortar and powder equivalent to 50 mg of LC was weighed and dissolved in 50 ml methanol. This was the stock solution from which 2 ml sample was withdrawn and diluted to 100 ml with phosphate-buffered (pH6.8). The absorbance was measured at wavelength 227 nm using double beam UV-Visible spectrophotometer.
6. Swelling Index: For the determination of swelling index, the tablets were kept for 12 h in Petri dish of 6.8 pH buffer solution. The swelling behavior of all the tablets after every 1 h the tablet was withdrawn, soaked with tissue paper and weight were noted.[15]
7. *In vitro* drug release studies:[6,16,20-22] *In vitro* dissolution test was carried out which indicates the mechanism and kinetics of drug release from a dosage form. This gives an idea of how the dosage form will behave when subjected to *in vivo* study. For the present work, *in vitro* dissolution studies were carried out in phosphate-buffer of pH 6.8 (900 ml) maintained at 37°C using dissolution test apparatus USP paddle type II model with a stirring rate of 50 rpm. 5 ml samples were withdrawn at each time interval, filtered, diluted, and analyzed for drug concentration to characterize dissolution profile.[6]

Results and Discussion

Preformulation studies

Characterization of lithium carbonate pure drug:

Melting point of the drug was noted in triplicate and was found to be 723°C which was similar to the pharmacopeial standards. Lithium carbonate is practically insoluble in distilled water and average solubility of the drug was found in phosphate-buffered pH 6.8. The UV spectrum of pure lithium carbonate was obtained and is shown in Figure 1. The wavelength of maximum absorbance (λ_{max}) was found to be 227 nm in phosphate-buffered PH 6.8.

IR spectroscopy:

IR spectra of pure lithium carbonate and pure HPMC were obtained which are shown in Figures 2 and 3 respectively.

IR spectrum of pure lithium carbonate:

Interpretation of IR spectrum of pure lithium carbonate: This indicated that functional group such as amino, carboxyl, C=C, and C-C1 is present.

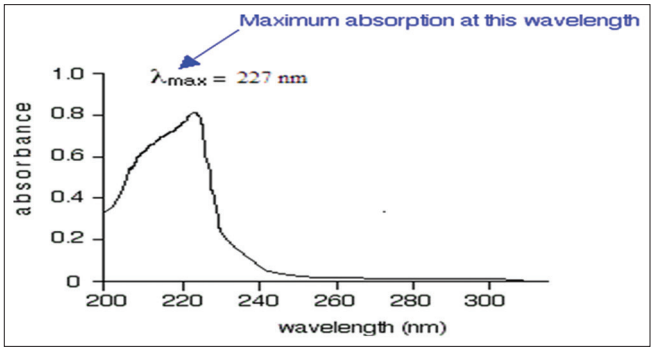

Figure 1: UV absorption spectrum of pure lithium carbonate

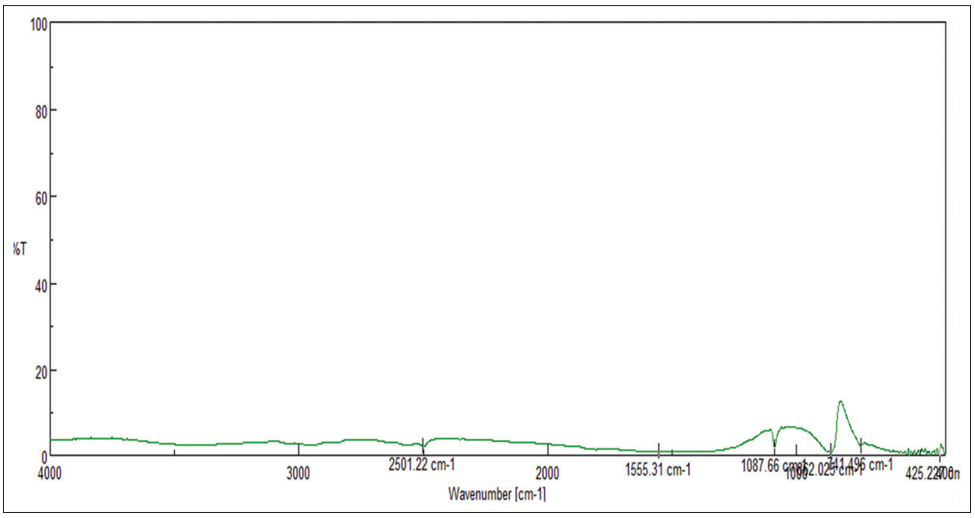

Figure 2: IR spectrum of pure lithium carbonate

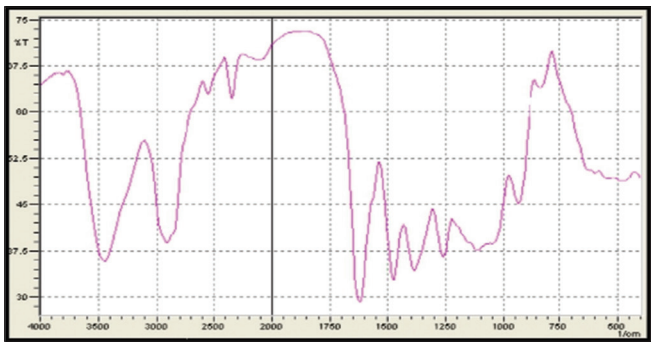

Figure 3: IR spectrum of pure HPMC

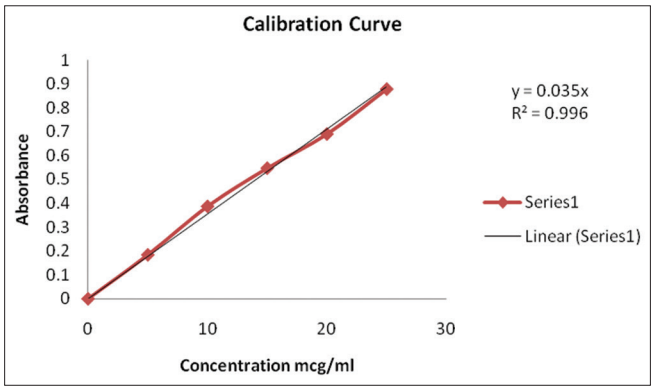

Figure 4: Standard curve for lithium carbonate

IR spectrum of pure HPMC:
Interpretation of IR spectrum of pure HPMC: This indicates that functional group such as hydroxyl, methyl hydroxypropyl, cyclic anhydride, and epoxide are present.

Method development and validation by UV spectroscopy

Preparation of standard curve (calibration curve) of lithium carbonate.

From the standard curve of lithium carbonate [Figure 4]; it was observed that the drug obeys beer's law in the concentration range of 0–30 μg/ml in phosphate-buffered pH 6.8. The linear regression equation generated was used for the calculation of amount of drug (y = 0.035x + 0.010).

Formulation of lithium carbonate matrix tablets

The procedure for formulation of sustained release matrix tablets of lithium carbonate is described earlier in methodology and tablet composition is given in Table 1 and weight of each tablet is 550 mg.

Evaluation of pre-compression properties of powder blend

1. Angle of repose: The values were found to be in the range from 270.10' to 320.56'. The results of repose angle studies indicated that the powders of all the formulations are freely flow able and easily compressible.
2. Bulk density: Bulk density for the entire formulation blend varied from 0.701 gm/cc to 0.869 gm/cc (wet granulation method).
3. Tapped density: Tapped density for the entire formulation blend ranges from 0.8 gm/cc to 1.00 gm/cc.
4. Compressibility index: Compressibility index value ranges between 8.31% and 12.03% indicating that the granules have the required flow property for compression. Compressibility index was found to be <17% for all the five formulations indicating that the powder is compressible.
5. Hausner's ratio: Hausner's ratio value ranges between 8.36 and 13.1 indicating that the granules have the required flow property for compression.

All the values are tabulated in Table 2.

Evaluation of the prepared formulation for physicochemical characteristics/tablet

The prepared tablets were subjected to preliminary characterization such as thickness, hardness%, weight variation, friability, and drug content.[6,16-19] Evaluation studies indicated that the values of

Table 2: Evaluation of pre-compression parameters

Formulation code	Angle of repose (θ)	Bulk density (g/cm³)	Tapped density (g/cm³)	Hausner's ratio	Compressibility index (%)
F1	32.67°	0.833	0.909	1.09	8.36
F2	31.82°	0.869	1.00	1.15	13.1
F3	32.41°	0.869	0.952	1.09	8.31
F4	29.35°	0.714	0.8	1.12	10.75
F5	28.34°	0.701	0.8	0.998	12.3

Table 3: Evaluation of post-compression parameters of matrix tablets of lithium carbonate

Formulation code	Hardness (kg/cm²)	Friability (%)	Weight variation (mg)	Thickness (mm)
F1	5.2±0.12	0.36	545±1	4.1±0.02
F2	5.9±0.25	0.36	547±2	4.3±0.01
F3	6.4±0.30	0.36	551±1	4.4±0.00
F4	7.0±0.21	0.34	550±1	4.0±0.02
F5	6.6±0.12	0.42	551±2	4.1±0.05

All values are expressed as mean±SD, n=5.

various parameters were within the pharmacopeial limits for all five formulations. All the values are tabulated in Table 3.

1. Tablet thickness: Tablets mean thicknesses were almost uniform in all the formulations and were found to be in the range of 4.3 mm–4.7 mm.
2. Hardness: The measured hardness of tablets of each batch ranged between 5.7 and 7 kg/cm². Tablet hardness was increased as increasing the compression force. This ensures good handling characteristics of all batches.
3. Weight variation test: All the tablets passed weight variation test as the % weight variation was within the pharmacopeial limits. The weights of all the tablets were found to be uniform with low standard deviation values.
4. Friability: The % friability was <1% in all the formulations ensuring that the tablets were mechanically stable.
5. Uniformity of drug content: The percentage of drug content was found to be between 98.29 and 100.21% of lithium carbonate, which was within acceptable limits.
6. Swelling Index[15,23]: All the five formulations showed increase in weight indicating that the polymer employed in the present investigation was having a capacity to swell the tablets. The percentage solution uptake ranged from 221.10 to 245 up to 14 h for all formulations. The values are shown in Figure 5.

Inference

This trend clearly indicates that as time increases the % swelling index also increases.

In vitro drug release studies

In vitro dissolution study was carried out using dissolution test apparatus USP paddle type II in 900 ml phosphate-buffered pH 6.8. These release studies revealed that among all formulations F4 formulation gives best release, i.e., 96.42% at 14 h and this batch

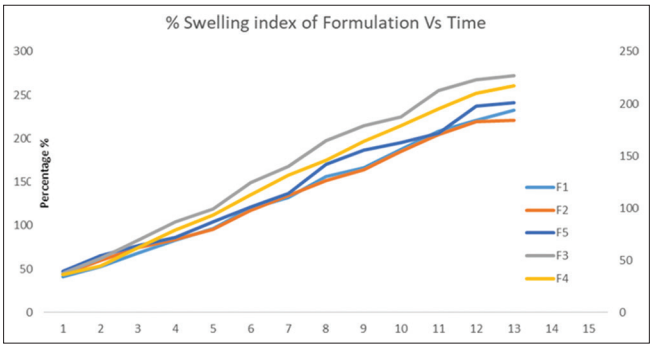

Figure 5: Trend chart for % swelling index versus time

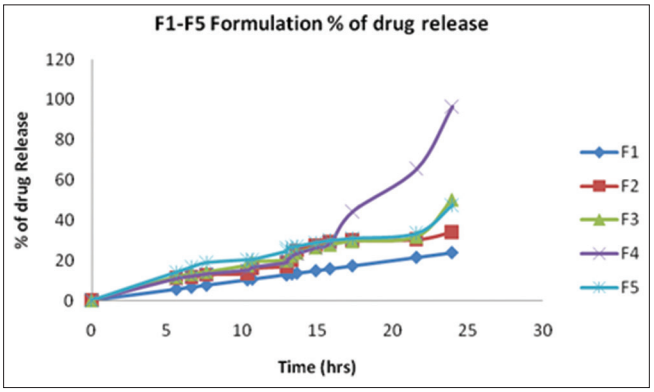

Figure 6: *In vitro* dissolution profile of formulations F1 to F5.

was selected as optimized batch. The *in vitro* dissolution release result of all formulations is given in Figure 6.

Conclusion

Lithium carbonate was successfully formulated as sustained release matrix tablet using hydrophilic polymer HPMC as release retardant. And in the present study, an attempt has been made to develop twice daily sustained release matrix tablets of lithium carbonate using HPMC so as to reduce the dosing frequency. The formulations provide sustained release of the drug over a period of 14 h *in vitro*. Among all the formulations our matrix formulation containing HPMC in the concentration 30% is probably showing better release based on the 96.42% of drug release within 14 h which is average G.I residence time.

Hence, this new formulation is a viable alternative to conventional LC tablets by virtue of its ability to enhance bioavailability through its sustained drug release and reduced frequency of administration resulting in better patient acceptance and compliance.

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