Research Paper

Preparation and Evaluation of Waxes/Fat Microspheres Loaded with Lithium Carbonate for Controlled Release

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To minimize the unwanted toxic effects of anti maniac drug lithium carbonate by kinetic control of drug release, it was entrapped into gastro resistant, biodegradable, waxes and fat such as beeswax, cetostearyl alcohol, spermaceti and cetylalcohol microspheres using meltable emulsified dispersion cooling induced solidification technique utilizing a wetting agent. Solid, discrete, reproducible free flowing microspheres were obtained. The yield of the microspheres was up to 90.0%. More than 98.0% of the isolated microspheres were of particle size range 115 to 855 μm. The microspheres had smooth surfaces, with free flowing and good packing properties. Scanning electron microscope confirmed their spherical structures within a size range of 339-355 μm. The drug loaded in waxes and fat microspheres was stable and compatible, as confirmed by DSC and FTIR studies. The release of drug was controlled for more than 8 hours. Intestinal drug release from waxes/ fat microspheres was studied and compared with the releases behavior of commercially available formulation Intalith CR®-450. The release kinetics followed different transport mechanisms. The drug release performance was greatly affected by the materials used in microsphere preparations, which allows absorption in the intestinal tract.

Lithium carbonate, a mono valent cation belonging to the group of alkali metals has been widely used in the treatment of bipolar and unipolar disorder[1]. Considering the long regimen of anti maniac therapy, the administration of lithium carbonate was reported to induce adverse side effects on GIT as well as hepatic, pancreatic, renal, endocrine, nervous, cardiac and hematological systems[2]. To achieve maximum therapeutic effect with a low risk of adverse effects, controlled released preparations are prefered[3]. The side effects could be lowered by controlling the drug release and by adjusting the absorption rate. This can be achieved by employing suitable modifications in the manufacturing proces[4,5]. Delivering the drug in the intestinal milieu from wax/fat microspheres could be manipulated by suitable coating techniques[6]. Extensive clinical experience and well-controlled studies have shown that lithium carbonate is more effective than chlorpromazine in the treatment of acute maniac phase of mixed bipolar disorder[7]. Major advantages of lithium carbonate over the other antipsychotics are decreased subjective sedation, lack of extra pyramidal reactions, absence of tardive dysksnesia and the biochemical specificity of lithium to normalize biochemical defects[8,9]. The chief characteristics of enteric coating are their impermeability to gastric juices but susceptibility to intestinal juices[10,11]. Lithium carbonate should be dosed at least three doses with a maintenance dose per day. Due to its low therapeutic index, the frequency of adverse effects may be dose related[12,13]. A controlled release dosage form of lithium salt is preferable than the conventional dosage form of lithium, because there is a considerable saving in nurses and pharmacists time[14]. As demonstrated by pharmacokinetic studies on lithium carbonate, the ingestion of a single controlled release enteric coated tablet is effective even when administered once a day[15]. These findings suggested that kinetic control is effective for preventing the toxicity of lithium carbonate.

Previous experimental results demonstrated that waxes are biocompatible, non-immunogenic material used for the entrapment of drug, used for controlling drug release in the intestinal tract[16,17]. The objectives of the present study are to formulate, characterize and study the *in vitro* drug release from wax/fat microspheres loaded with lithium carbonate. The pattern of drug release from the wax/fat microspheres is compared with that of the commercially

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available enteric-coated oral formulation, Intalith CR® - 450.

MATERIALS AND METHODS

Lithium carbonate USP Grade was a gift sample from Micro Labs, Bangalore, India. Spermaceti was generously gifted by British Drug House, Chemical Division, Poole, England. Beeswax, cetostearyl alcohol, cetylalcohol, span 20, Tween 80 and all the other chemicals and reagents were of analytical grade and were purchased from Loba Chemie Pvt. Ltd., Mumbai, India. Data analysis was carried out using PCP Disso-V2-08 and Graph Pad Instat software.

Preparation of waxes and fat microspheres:
9 g of waxes (beeswax, cetostearyl alcohol, spermaceti) and fat (cetylalcohol) were melted separately in china dishes using water baths. Three grams of drug previously passed through sieve no.100 was dispersed each one in the melted wax/fat mass and stirred to obtain a homogeneous melt. These individual mixtures were poured into 150 ml of pH 10.9 Ammonia buffer solution (to minimize the solubility of drug), which was previously heated to a temperature higher than melting point of wax/fat (>+ 5°). Tween 80 (1.8% w/w) was added to the mixtures containing beeswax, cetostearyl alcohol, cetylalcohol and span 20 (2.0% w/w) for the mixture containing spermaceti. The whole mixture was mechanically stirred at 900 rpm using a stirrer (RQ-127A) fitted with a 4- blade impeller of approximately 53 mm diameter. Spherical particles are produced due to dispersion of molten wax/fat in the aqueous medium. The mixture was stirred continuously at 900 rpm at a higher temperature (>+ 5°) of the melting point of wax/fat for 2 min. The temperature of the mixture in the beakers was cooled rapidly to 10° by the addition of cold water. The resultant solid spheres collected by filtration were extensively washed with water to remove any drug and surfactant residues. Air drying was carried out at room temperature for 48 h gave discrete, solid, free flowing microspheres.

Size distribution and size analysis of microspheres:
Size distribution of the wax/fat microspheres was studied by sieve analysis technique. The separations of the microspheres in to various size fractions were carried out and SEM analyzed the size of microspheres.

Micromeritic properties:
Tap density of the prepared microspheres was determined using tap density tester and % Carr's index (%I) was calculated. Angle of repose was assessed to know the flowability of waxes/fat microspheres, by a fixed funnel method.

Scanning electron microscopic (SEM) study:
SEM photographs were taken using scanning electron microscope Model Joel- LV-5600, USA, at suitable magnification at room temperature. The photographs were observed for morphological characteristics and to confirm spherical nature of the microspheres.

Determination of the sphericity:
To determine the sphericity, the tracings of waxes/fat microspheres (magnification 45 X) were taken on a black paper using Camera Lucida, (Model-Prism type, Rolex, India) and circulatory factor was calculated[18]. The sphericity of microspheres was calculated using the equation, $S = p^2/(12.56 \times A)$, where A is area (cm^2) and p is perimeter (cm).

Differential scanning calorimetry (DSC):
All dynamic DSC studies were carried out on DuPont thermal analyzer with 2010 DSC module. Calorimetric measurements were made with the help of an empty cell (high purity alpha alumina discs of DuPont Company) as the reference. The instrument was calibrated using high purity indium metal as standard. The dynamic scans were taken in nitrogen atmosphere at the heating rate of 10°/min. The runs were made in triplicate.

Fourier transform infrared radiation measurements (FTIR):
The samples (2 mg of the pure drug, empty microspheres and drug loaded microspheres) were selected separately and dispersed in KBr powder; the pellets were made by applying 6000 kg/cm^2 and analyzed. Spectral measurements were obtained by powder diffuse reflectance on a FT-infrared spectrophotometer type Shimadzu, Model 8033,USA.

Estimation of drug loading:
Drug incorporated wax/fat microspheres of each batch were selected and powdered in a mortar. Drug was extracted from wax/fat microspheres using 0.1 N HCl, filtered and analyzed for drug content after suitable dilution.

***In vitro* studies:**
USP XX1 dissolution apparatus type II was employed to study percentage of drug release from various formulations

prepared. Encapsulations of the drugs-loaded microspheres were avoided, as dissolution of shell will add one more parameter to the result. Accurately weighed quantities of drug (lithium carbonate - 450 mg equivalent to a commercial preparation - Intalith CR®-450 mg tablet,) loaded microspheres of each batch were taken in 900 ml dissolution medium (lithium carbonate - 2 h in pH 1.2 hydrochloric acid buffer and 6 h in pH 7.4 tris chloride buffer BET) and stirred at 100 rpm by maintaining at a temperature of 37±0.5°. The drug concentrations were determined by withdrawing the 10 ml of aliquots using guarded sample collectors periodically at an interval of 30 min for first 4 h and at 60 min interval for the next 4 h. Release studies were carried out in triplicate.

RESULTS AND DISCUSSIONS

Evidence have[16,17] shown in the recent years that waxes and fat materials have the physical properties and behavior suitable to prepare gastro resistant, biocompatible, biodegradable microspheres to release the entrapped drug in the intestinal lumen[10,11,19]. In the present study, a modified novel meltable dispersion emulsified cooling induced solidification method was employed using inert waxes/fat (FDA approved) material and non-toxic solvents to entrap the drug. The present method is quite different from that reported by Giannola *et al*[20]. Because in the present study, various parameters were modified such as drug and wax/ fat ratio, stirring speed and time, amount of surfactant added, volume of the aqueous phase used, effect of pH on drug entrapment, temperature of the aqueous phase, rapid cooling studies, different types of waxes and fats having wide range of molecular weight were used during the preparation of wax/fat microspheres which are not studied and reported method[20]. Therefore the influence of the above parameters was highlighted. When the pH value of the external aqueous phase was highly alkaline, the solubility of the drug was reduced and the encapsulated amount of the drug increased. The maximum drug load was obtained at pH 10.9. When pH value changes from 10.9 to 7.2, the percent of drug loading reduced from 12.76 to 4.64%, 14.46 to 4.87%, 10.88 to 4.38% and 13.86 to 4.76% for drug loaded beeswax, cetostearyl alcohol, spermaceti and cetylalcohol microspheres, respectively. Incorporation of drug into wax/fat microspheres required the addition of a surfactant at an optimum concentration to reduce the interfacial tension between the hydrophobic material and external aqueous phase. An attempt was made to incorporate drug in the waxes/fat microspheres without the addition of a surfactant. But the process was a failed, as it resulted in an aggregate cake like mass during the solidification of waxes/ fat. This may be due to repulsion resulting from high interfacial tension between the hydrophobic waxy/fat material and external aqueous phase. To obtain an optimal surfactant concentration, various concentrations ranging from 0. 5 to 2.0% (w/w) of the total formulation were tested. Discrete microspheres with good flow properties using an optimum concentration of surfactants 1.8% w/w (Tween-80) for beeswax, cetostearyl alcohol, cetylalcohol and 2.0% w/w (Span-20) for spermaceti were obtained. Concentrations of surfactant (Tween 80) ranging from 0.5 to 1.7% w/w in case of beeswax, cetostearyl alcohol, cetylalcohol and 0.5 to 1.9% w/w (Span-20) in case of spermaceti did not give reproducible microspheres. The resultant waxes/fat microspheres were composed of irregular masses, which were not possible to distinguish as individual microspheres.

In the present study, it was found that 150 ml of aqueous phase suitable for producing the spherical microspheres. Resultant microspheres did not have any surface irregularities and are non aggregated. As the volume of external phase increased, the yield was reduced and the resultant microspheres were irregularly shaped. When the volume of the aqueous phase was less than 150 ml, the resultant microspheres were highly aggregated in nature and highly impossible to distinguish as an individual microspheres. In order to avoid the formation of irregularly shaped larger particles, in the present method, 150 ml of aqueous phase was used.

Temperature of the aqueous phase was maintained at 5^0 higher than the melting point of the waxes/fat in the corresponding formulations. From SEM studies it was observed that the resultant microspheres were free from surface irregularities, except some wrinkles. It was also observed that when the temperature of the aqueous phase was less than the 5^0 than the melting point of the wax / fat, big flakes were produced.

Sah[21] developed microspheres using a phase ratio 1:10, but the obtained microspheres were irregular in shape and were highly aggregated. By using a phase ratio 1:3, Giannola *et al*[20] have developed spherical microspheres by using wax, but these were not hallow in nature. In the present study, to produce the spherical discrete microspheres, an optimum drug to waxes/fat phase ratio of 1:3 w/w was used. It was found that higher the amount of drug to waxes/fat ratio (2:3) produces aggregate masses during the cooling process. It may be due to reduced melting point of the waxy and fat materials. SEM photographs also indicated the presence of the crystals

on the surface of the microspheres. The resultant microspheres were unsuitable for pharmaceutical uses.

Sieve analysis data indicated that the prepared microspheres were in the size range of 106 to 500 mm and 56.3 to 63.6% were of size fraction 250 μm shown in Table 1. It was observed that the average size of the microspheres ranged between 339 to 357 μm presented in Table 2. The sizes of the drug loaded beeswax and spermaceti microspheres were larger than cetostearyl alcohol and cetylalcohol microspheres. It was found that surfactants having a HLB value of 15 are more suitable to increase substantial dispersion of beeswax, cetostearyl alcohol, and cetylalcohol in aqueous media, HLB of 8.6 for spermaceti that promoted drug incorporation in the microspheres. Solid, discrete, free flowing microspheres were produced, after cooling. A similar surfactant concentration was reported for beeswax microspheres prepared by a meltable dispersion method[20].

The important factor that influences the size distribution of microspheres is the optimum stirring speed and stirring time. A stirring speed of 900 rpm and stirring time of 2 min was used to obtain reproducible microspheres. It was observed that with the increase in the stirring speed from 900 to 1100 rpm there was a decrease in the average size of the spheres and recovery yield of the microspheres. It is due to small sized waxes/fat microspheres, which were lost during successive washings. When the stirring speed was lower than 900 rpm, larger pellets were a formed. It was also found that an increase in stirring time, from 2 to 4 min (at a stirring speed of 900 rpm), there was a decrease in the recovery yield of microspheres. When the stirring time lower than 2 min, it was observed that some amount of melted material adhered to the sides of the beaker during the cooling process resulting in lower recovery of yield. Repeat batches treated at an optimized rate mentioned above proved to produce reproducible sizes, showing that stirring speed and stirring time were well controlled.

Generally the micro particulate drug delivery systems are formulated as single unit dosage forms in the form of capsule or tablet. Such microparticulate systems should possess the better and adequate micromeritic properties. The values of ϕ indicate reasonable good flow potential for the microspheres. The tapped density values ranged between 0. 4347 g/cm^3 to 0. 5 g/cm^3. The results of % of I ranges from 8.24% to 20.07%, suggests good flow characteristics of the microspheres (Table 2). The better flow property indicates reasonable and good flow potential of prepared microspheres.

SEM photographs showed that the wax/fat microspheres were spherical in nature, had a smooth surface with inward dents and shrinkage, which is due to the collapse of the wall of the microspheres (fig. 1). SEM photographs

TABLE 1: SIZE DISTRIBUTION OF WAXES/FAT MICROSPHERES.

Formulations	Size Range (μm)					
	710	500	250	150	125	106
AL	-	12.3	63.6	14.1	7.2	2.1
BL	-	12.6	61.7	13.0	9.0	3.7
CL	-	6.5	56.3	18.9	13.4	4.9
DL	-	14.3	59.6	13.4	9.8	2.9

Values shown in the table mean percent of 3 batches (n=3), LC is lithium carbonate, AL is beeswax+LC, BL is cetostearyl alcohol+LC, CL is spermaceti+LC and DL is cetylalcohol+LC.

TABLE 2: MICROMERITIC PROPERTIES OF THE DRUG LOADED WAX /FAT MICROSPHERES

Formulations	Size (μm)	Yield %	Angle of repose θ°	%I	Tapped density g/cm3
AL	357	90.75	27.99	12.64	0.4347
BL	342	86.92	26.95	8.24	0.4347
CL	355	85.67	28.81	15.60	000.5
DL	339	86.67	27.24	20.17	0.4347

Values shown in the table mean percent of 3 batches (n=3), LC is lithium carbonate, AL is beeswax+LC, BL is cetostearyl alcohol+LC, CL is spermaceti+LC and DL is cetylalcohol+LC.

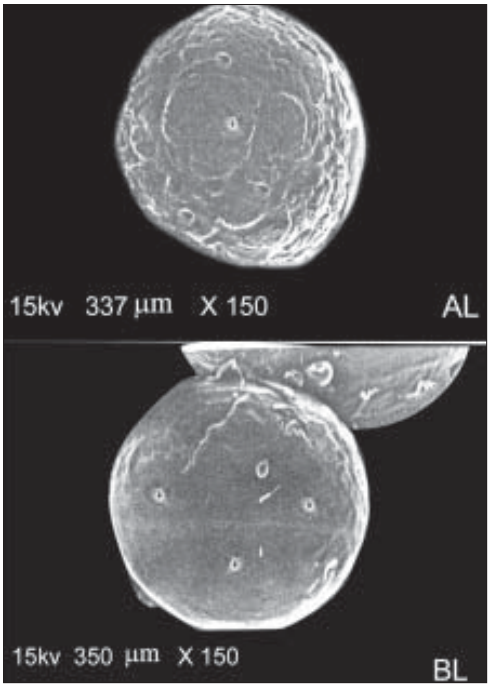

Fig. 1: SEM photographs of waxes/fat microspheres loaded with lithium carbonate showing surface dents and spherical in nature.

reveal the absence of crystals of the drug on the surface of microsphere, indicating uniform distribution of the drug within the microspheres and further indicate that low molecular weight wax/fat produce better quality microsphere than that of high molecular weight waxes. The rate of solvent removal from the microspheres exerts an influence on the morphology of the final product[22]. The sphericity factor obtained for the microspheres nearer to the value 1, confirming the sphericity of the microsphere.

DSC studies were performed on pure drug, empty and drug-loaded microspheres have shown sharp endothermic peaks. Lithium carbonate exhibits a sharp endothermic peak at 618° presented in fig. 2. It was observed that absence of the endothermic peak of the drug at 618° in the drug loaded waxes/fat microspheres indicates, that the drug is uniformly distributed at molecularly level in the microspheres[23].

From the FTIR studies, the characteristic bands for important functional group of pure drug empty microspheres and drug-loaded microspheres were identified. FTIR spectra showed that the characteristics bands of lithium carbonate were not altered after successful encapsulation without any change in their position, indicating no chemical interactions between the drug and waxes/fat used. Henry[24] compared the IR spectra at 2915 cm^{-1} due to CO_3 stretching, 1715 cm^{-1} due to C=O stretching, 1081 cm^{-1} OH deformation and 860 cm^{-1} due to corboxylate ion stretching. A comparison and interpretation of this region in our spectra agrees with their conclusions. The percent of drug loading in the formulations were in the range of 10.88% to 14.46%. It was low in the formulations prepared by using spermaceti and high for cetostearyl alcohol as shown in Table 3.

From the release studies it was observed that, there is no significant release of drug at gastric pH from wax/fat microspheres. At the end of 8th h, *in vitro* drug release from cetostearyl alcohol (84.68%), cetylalcohol (78.49%) microspheres was faster than beeswax (75.83%), spermaceti (67.75%) microspheres in the intestinal environment as shown in fig. 3. The decreased *in vitro* drug release from beeswax, spermaceti microspheres was slower than that of cetostearyl alcohol, cetylalcohol microspheres might be due to more hydrophobicity and influence of molecular weight of waxes/fat. The *in vitro* drug release was considerably retarded from the waxes/fat microspheres when compared Intalith CR®-450. The rate of drug release followed first order release kinetics and numerical data fitted into Peppa's equation[25] showed that the mechanism of drug release from cetostearyl alcohol, cetylalcohol microspheres was Fickian diffusion and non-Fickian diffusion from

TABLE 3: DRUG LOADING PROPERTIES OF WAX/FAT MICROSPHERES

Formulations	Loading (%)	Encapsulation efficiency (%)
AL	12.76	51.04
BL	14.46	57.87
CL	10.88	43.53
DL	13.86	56.44

Values shown in the table mean percent of 3 batches (n= 3), lithium carbonate (LC), AL (beeswax + LC), BL (cetostearyl alcohol+LC), CL (spermaceti+LC), DL (cetylalcohol+LC).

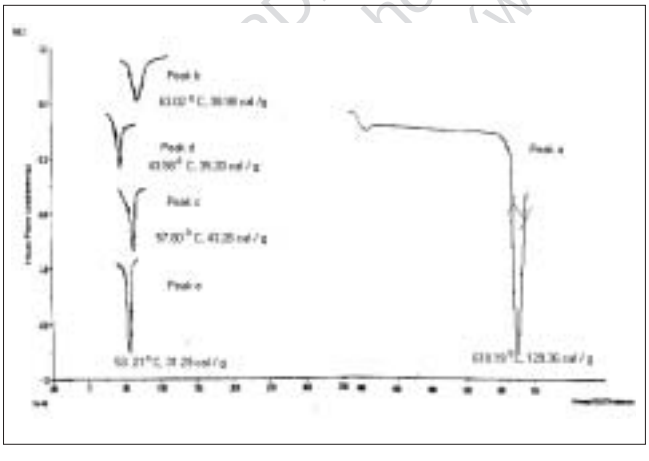

Fig. 2: DSC thermograms obtained for pure drug LC, and microspheres AL, BL, CL and DL
Peak a is for pure lithium carbonate LC, peak b is for AL, which is LC loaded in beeswax. Peak c is for BL, which is LC loaded in Ccetostearyl alcohol, peak d is for CL, which is LC loaded in spermaceti and peak e is for DL, which is LC loaded in cetylalcohol.

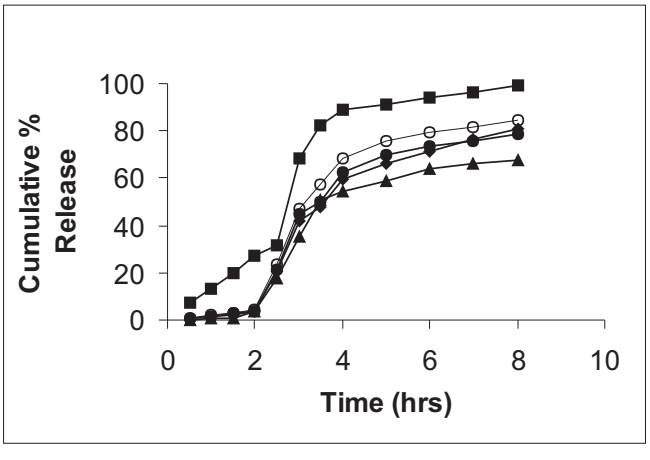

Fig. 3: Cumulative % release of lithium carbonate (LC) from waxes/fat microspheres and Intalith-CR-450 in the gastric and intestinal environment against the time.
Release of lithium carbonate from beeswax (-◆-), cetostearyl alcohol (-o-), spermaceti (-▲-), cetylalcohol (●) microspheres and Intalith-CR-450 (-■-)

TABLE 4: *IN VITRO* RELEASE KINETIC PARAMETERS, DIFFUSION COEFFICIENTS (D_1 AND D_2) FOR WAXES/ FAT MICROSPHERES

Formulations	n	k (min^{-n}) 10^2	Molecular weight	D_1 cm^2/ h	D_2 cm^2/ h
AL	0.57	1.50	438	1.12	3.80
BL	0.45	1.63	260	1.45	4.21
CL	0.50	1.48	480	1.00	3.19
DL	0.62	1.56	242	1.32	3.95

Values shown in the table mean percent of 3 batches (n=3), LC is lithium carbonate, AL is beeswax+LC, BL is cetostearyl alcohol+LC, CL is spermaceti+LC and DL is cetylalcohol+LC.

beeswax, spermaceti microspheres (Table 4). After an initial burst effect, the subsequent release was slow, and the influence of molecular weight (MW) was observed (Table 4). We found a small variation in the value of k. For instance, k = 0.0163 for cetostearyl alcohol, while it was smaller about 0.0148 for spermaceti. Intermediate values of k 0.0150 for beeswax and 0.0156 for cetylalcohol microspheres was observed.

The diffusion coefficients for D_1 vary from 1.12-to 1.45-cm^2/h and D_2 3.19 to 4.21 cm^2/h. Higher values of D were obtained for the drug loaded cetostearyl alcohol and cetylalcohol when compared to the drug loaded beeswax and spermaceti microspheres. The D values also show a decreasing trend with an increase in MW of the microspheres.

The drug release was found sufficient for oral delivery of drug. The drug release profiles were significantly affected by the properties of waxes/fatty materials used in the preparation of microspheres. These results demonstrate the potential use of waxes/fat for the fabrication of controlled delivery devices for many water soluble or hydrophilic drugs.

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