Research Article

Preparation and *In Vitro* Evaluation of Lamivudine Floating Sodium Alginate Beads

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ABSTRACT

The objective of the study was to develop a oral controlled release drug delivery system of lamivudine using non effervescent approach with hydrocolloid gel forming agent HPMC (hydroxylpropyl methylcellulose) and sodium alginate. Alginate beads of lamivudine were prepared by ionotropic gelation method. The prepared alginate beads were subjected to evaluation for particle size, incorporation efficiency and in vitro drug release characteristics. Alginate beads were discrete spherical and free flowing with smooth surfaces and completely covered with polymer coat. The alginate beads produced were smooth and small in size with an average diameter of about $506.19\pm7.2\mu m$ to $537.31\pm8.6\mu m$. The prepared floating alginate beads were exhibited prolonged drug release (~12 hrs) and remained buoyant for greater than 12hrs.The release kinetics showed that the release of drug from the beads followed zero order kinetics. Drug release was controlled by diffusion from the alginate beads that was slow and spreads over an extended period of time depending upon the drug polymer ratio.

Keywords: Floating alginate beads; Lamivudine; Sodium alginate; HPMC; In vitro release

INTRODUCTION

In recent years, considerable attention has been focused on the development of controlled drug delivery systems. The basic rationale of controlled drug delivery system is to optimize the biopharmaceutic, pharmacokinetic and pharmacodynamic properties of a drug in such a way that its utility is maximized through reduction in side effects and cure or control the conditions in the shortest possible time by using smallest quantity of drug administered by most suitable route (1). Controlled drug delivery system release the drug according to zero order rate in which the amount of drug released to the absorption site remains reasonably constant over a prolonged period of time. Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. Gastro-retentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. The drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration. Floating microspheres to improve patient compliance by decreasing dosing frequency, better therapeutic effect of short half-life drugs can be achieved. Enhanced absorption of drugs which solubilize only in stomach, gastric retention time is increased because of buoyancy. Gastric emptying of dosage form is extremely variable process and ability to prolong and control the emptying time is valuable asset for dosage forms, which reside in the stomach for a long period of time than conventional dosage forms. Several difficulties are faced in designing controlled released systems for better absorption and enhanced the bioavailability (2). Conventional oral dosage forms such as tablets, capsules provide specific drug concentration in systemic circulation without offering any control over drug delivery and also cause great fluctuations in plasma drug levels. Although single unit floating dosage forms have been extensively studied, these single unit dosage forms have the disadvantage of a release all or nothing emptying process while the multiple unit particulate system pass through the GIT to avoid the vagaries of gastric emptying and thus release the drug more uniformly. Several controlled oral drug delivery systems with prolonged gastric residence times have been reported recently such as: floating drug dosage systems (FDDS) (3-7), swelling or expanding systems (8), mucoadhesive systems (9-10), modified-shape systems (11), high-density systems (12), and other delayed gastric emptying devices. Among these systems, FDDS have been most commonly used. The uniform distribution of these multiple unit dosage forms along the GIT could result in more reproducible drug absorption and reduced risk of local irritation; this gave birth to oral controlled drug delivery and led to development of Gastro-retentive floating microspheres (13-14). Highly swellable hydrocolloids and light mineral oils (15-16). Multiple unit systems (17-19), and hollow systems prepared by solvent evaporation methods (20-22), have also been developed.

Non-Effervescent Systems developed with hydrocolloids as hydrodynamically balance system was first designed by Sheth and Tossounian in 1975. Such systems contains drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. This system incorporate a high level of one or more gel forming highly swellable cellulose type hydrocolloids e.g. HEC, HPMC, NaCMC, Polysacchacarides and matrix forming polymers such as

polycarbophil, polyacrylates and polystyrene, incorporated either in tablets or in capsules. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around the gel surface. The air trapped by the swollen polymer maintains a density less than unity and confers buoyancy to these dosage forms (23). Alginate beads of lamivudine prepared with sodium alginate and HPMC comes under the category of non-effervescent Systems.

Mechanism of floating microspheres : When microspheres come in contact with gastric fluid the gel

acetic acid, calcium chloride used was of analytical grade and procured from authorized dealers.

Preparation of alginate beads: Alginate beads of lamivudine were prepared by ionotropic gelation method. Sodium alginate and HPMC were dissolved in distilled water with gentle agitation followed by the addition of 0.5gms of calcium carbonate. The mixture was kept aside for 5 minutes for the escape of air bubbles. Then drug (100mg) was added and mixed thoroughly. This solution was extruded into 1% w/v calcium chloride solution containing 10% w/v acetic acid. The beads were

$$Percentage\ Yield = \frac{Weight\ of\ Microsphere\ recovered}{Weight\ (drug + Polymer)}\ X\ 100$$

formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the microspheres. However a minimal gastric content needed to allow proper achievement of buoyancy (24-25). The present research work based on non effervescent approach using hydrocolloidal gel forming agent and sodium alginate as a interlocking agent. The model dug taken was lamivudine.

Lamivudine is a synthetic nucleoside analogue that is being increasingly used as the core of an antiretroviral regimen for the treatment of HIV infection. Lamivudine is rapidly absorbed after oral administration with an absolute bio availability of 86% ± 16% and mean elimination half life of 5 to 7 hours, thus necessitating frequent administration to maintain constant therapeutic drug levels. Microspheres would be capable of reducing the frequency of administration and the dose dependent side effects associated with the repeated administration of conventional lamivudine tablets (26).

MATERIALS AND METHODS

Materials: Lamivudine was received as a gift sample from Aurobindo Pharma Private Limited, Hyderabad. Sodium alginate used was available from SD Fine chem. Ltd, Mumbai. HPMC was commercially obtained from Hi media laboratories, Mumbai. Calcium carbonate was obtained from Qualigens fine chemicals, Mumbai. Glacial

collected and washed with distilled water and dried in an oven. Alginate beads formulated with different ratios of Sodium alginate and HPMC like F1(720:180), F2(750:150), F3(760:140), F4(770:130), F5(780:120), F6(790:110), F7(800:100), F8,(810:90),F9 (820:80), F10(850:50).

Evaluation of alginate beads: Percentage yield and drug entrapment efficiency (DEE) (27).

The alginate beads were evaluated for percentage yield and percent drug entrapment. The yield was calculated as per equation – 1.

Drug loaded alginate beads (100mg) were powdered and suspended in 100ml methanol: Water (1: 99v/n) solvent system. The resultant dispersion was kept for 20 min for complete mixing with continuous agitation and filtered through a 0.45 μm membrane filter. The drug content determined spectrophotometrically (UV systronics – 117) at 270 nm using a regression equation derived from the standard graph (r^2 = 0.9978). The drug entrapment efficiency (DEE) was calculated by the equation.

$$DEE = \left[\frac{Pc}{Tc}\right]\ X\ 100$$

Pc is practical content
Tc is the Theoretical content. All the formulations were analyzed in triplicate (n=3).

Particle size analysis: The size of the prepared microspheres was measured by the optical microscopy method using a calibrated stage micrometer. Particle size was calculated by using equation.

λg = 10 X [(ni x log xi) / N]

λg is geometric mean diameter.

Table 1. Evaluation parameters of various formulations

Formulation code	Buoyancy (%)	Floating lag time(sec)	Yield (%)	Particle size(μm)	DEE
F1	77.22 ± .6	16.6 ± 2.0	95.16±0.3	532.14±10.3	73.59±1.9
F2	76.21 ± .3	15.3 ±1.5	96.56±0.2	520.17 ± 8.2	76.64±1.4
F3	68.97 ± .7	15 ± 1.5	94.5 ±0.3	537.31± 8.6	82.08±1.8
F4	72.7 ± .7	15.6 ± 2.0	97.2 ±0.3	512.75±11.0	68.38±2.5
F5	73.08 ± 1.2	15 ± 2	95.83±0.2	532.17 ± 7.7	73.34±1.5
F6	80.41 ± .3	15.6 ± 1.5	97.4 ±0.3	518.75± 8.9	83.04±2.5
F7	84.87 ± .7	14.6± 2.5	98.1±0.3	506.19 ± 7.2	89.60±2.4
F8	71.57 ±1.0	15.6 ± 1.5	96.16±0.2	513.9 ± 7.1	84.32±2.5
F9	78.58± .4	15.6 ± 3.2	95.06±0.2	519.89 ± 7.5	65.9±1.8
F10	72.41 ± .06	14.6 ± 3.0	96.33±0.2	533.02 ± 5.9	78.31±3.2

Figure-1. SEM photographs of F7 formulation of lamivudine floating alginate beads
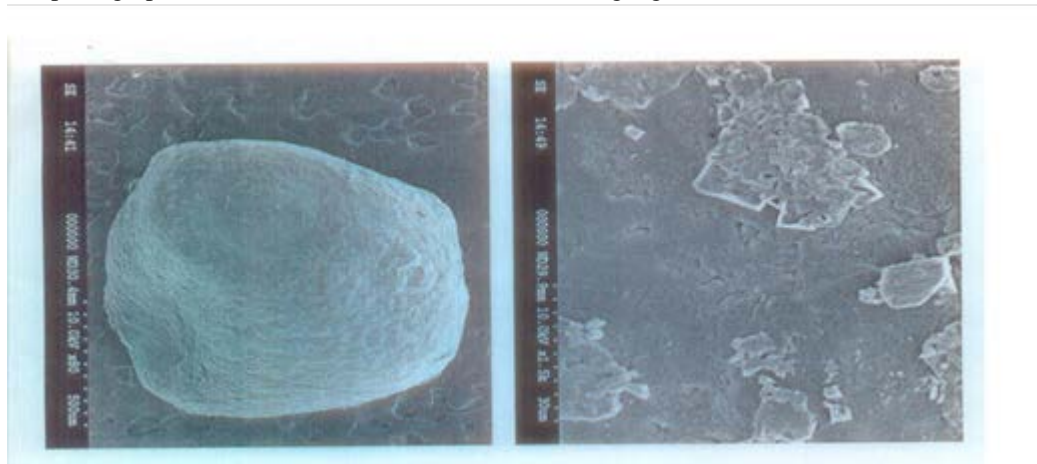
ni is number of particles in range.

xi is midpoint of range.

N is the total number of particles. All the experimental units were analyzed in triplicate (n=3).

In vitro drug release: In vitro drug release study was carried out in USP XII paddle type dissolution apparatus using 0.01 M HCl (pH 1.2) as dissolution medium. Volume of dissolution medium was 900 ml and bath temperature was maintained at 37 ± 1^0C throughout the study paddle speed was adjusted to 50 rpm. At an interval of 1 hour, 5 ml of sample was withdrawn with replacement of 5 ml fresh medium and analyzed for drug content by UV-visible spectrophotometer at 270 nm (28).

In vitro drug release kinetics: In order to study the exact mechanism of drug release from the alginate beads, drug release data was analyzed according to zero order, first order, Higuchi square root, Hixon – Crowell and Korsmeyer Peppas equation. The criteria for selecting the most appropriate mode were chosen on the basis of goodness of fit test.

Floating behavior: Floating alginate beads (100 mg) were spread over the surface of USP XII paddle type dissolution apparatus using 0.01 M HCl (pH 1.2) as dissolution medium. The medium was agitated with a paddle rotating at 100 rpm for 12 h. After 12 hours, the layer of buoyant alginate beads was pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in desiccators until constant weight was achieved. Both the fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles.

Buoyancy (%) $= W_f (W_f + W_s) \times 100$

Where W_f and W_s) are the weights of the floated and settled alginate beads, respectively. All the determinations were made in triplicate (29-30).

Floating lag time: In a beaker 100 ml of 0.01 M HCl was taken and 100 mg of alginate beads were dropped in the beaker. The stopwatch was started and the time duration was noted till the microspheres reached the top of the fluid in the beaker.

Accelerated stability studies: Stability studies were performed according to ICH guidelines. The F7 formulation was stored in room temperature at $25 \pm 1°$, in hot air oven at $37 \pm 1°$, and at $60 \pm 1°$ for a period of 14 weeks. The samples were analyzed for drug content every two weeks by spectrophotometer at 270 nm and compatibility of drug with excipients was determined by infrared spectroscopy.

Fourier Transforms Infrared Radiation measurement (FT-IR): The FT-IR spectra acquired were taken from dried samples. A FT-IR (Shimadzu IR spectrophotometer, model 840, Japan) was used for the analysis in the frequency range between 4000 and 600 cm-1, and 8 cm-1 resolution and a 0.2 cm-1 rate. A quantity equivalent to 2 mg of pure drug, empty microspheres of sodium alginate, HPMC and drug loaded microspheres were selected separately.

RESULTS AND DISCUSSION

Floating microspheres were prepared by the ionotropic gelation method using HPMC and sodium alginate.

Percentage yield and drug entrapment efficiency (DEE): The percentage yield of all the formulations was found to be satisfactory and each formulation exhibited high drug entrapment efficiency (DEE), as summarized in Table-1. The formulation F7 showed higher DEE (89.60±2.4) and higher yield (98.1±0.3) among all the formulations.

Particle size analysis: The prepared beads were analyzed by optical microscopy and scanning electron microscopy for their surface and size analysis. The SEM picture shows the presence of oil droplets throughout the alginate matrix. The initial burst effect seen was due to some amount of the drug, which might have been dragged to the surface during the processing. When calcium ions are added to a sodium alginate solution, alignment of the G blocks occurs; and the calcium ions are bound between the two chains like eggs in an egg box. Thus the calcium reactivity of algins is the result of calcium-induced dimeric association of the G block regions. Depending on the amount of calcium present in the system, these inter-chain associations can be either temporary or permanent. With low levels of calcium, temporary associations are
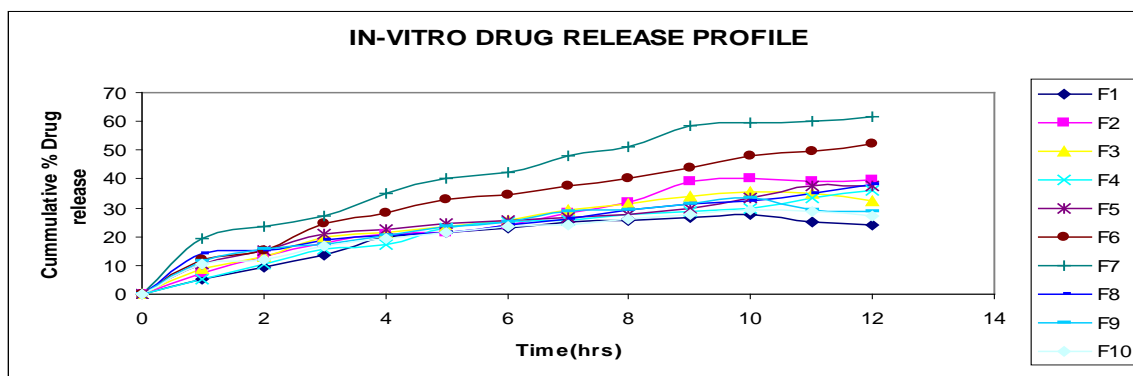
Figure-2.Drug release profile of lamivudine floating alginate beads
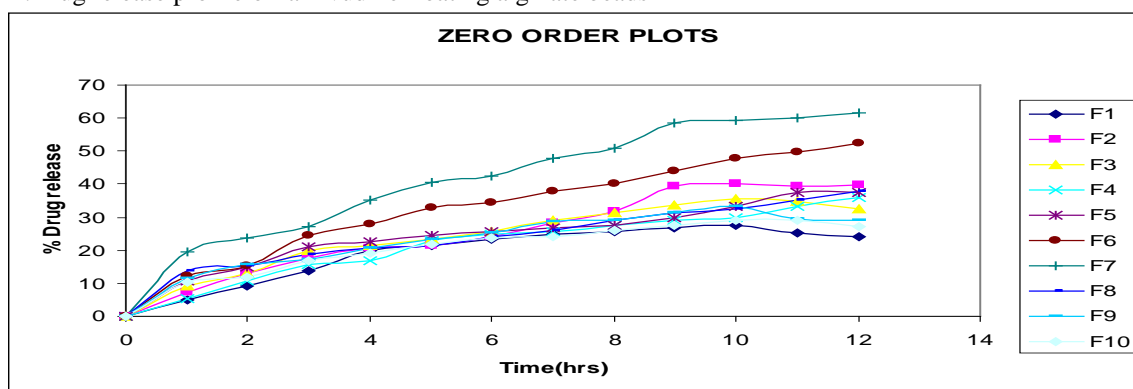

Figure-3. In vitro drug release kinetics of lamivudine floating alginate beads – zero order plot.

Table 2. Correlation coefficients according to different kinetic equations

Formulation Code	ZeroOrder(r^2)	First Order(r^2)	Higuchi(r^2)	Koresmeyer(r^2)
F1	0.7724	0.6778	0.9059	0.768
F2	0.9553	0.6921	0.9602	0.7806
F3	0.8804	0.7762	0.9742	0.7009
F4	0.9393	0.7841	0.9783	0.8079
F5	0.9023	0.7596	0.9811	0.6525
F6	0.9497	0.8963	0.9889	0.7047
F7	0.9308	0.8542	0.9878	0.6256
F8	0.9224	0.8736	0.9802	0.9658
F9	0.8101	0.8415	0.949	0.6182
F10	0.8433	0.7159	0.9734	0.6425

obtained, giving rise to highly viscous, thixotropic solutions. At higher calcium levels, precipitation or gelation results from permanent associations of the chains.

The SEM photographs (figure-1) showed that the fabricated microspheres were spherical with smooth surface and exhibited a range of sizes within each batch. Microspheres were prepared using different ratios of sodium alginate and HPMC to assess the effect of polymer concentration on the drug release of microspheres. The mean particle size of the microspheres was in the range 506.1±7.2µm to 537.3±8.6µm (Table-2). No significant differences in particle size were found for all the microspheres. Small variations may be attributed to different conditions, like agitation speed and agitation time or fluctuations in temperature.

In vitro drug release: The in vitro drug release profiles for all the formulations were graphically represented in Figure-2. The cumulative release of lamivudine increased with increasing sodium alginate concentration and decreased HPMC concentration up to certain level, after that the drug release was decreased

In vitro drug release kinetics: When a drug is incorporated in a hydrophilic matrix, it swells upon ingestion and the gel layer forms on the surface. This gel layer fills the interstices. Dissolution rate of soluble drugs is controlled by both diffusion through the gel layer and by matrix erosion as seen from the release kinetics values (Table 2). The data show that the release mechanism is chiefly by zero order kinetics.

All the formulations showed constant release profile to identify the kinetics of drug release from microspheres, release data was analyzed according to different kinetic models. The data obtained for *In vitro* release were fitted into equations for the zero order, first order, Hixon – Crowell, Higuchi and Korsmeyer Peppas release models.

Table 3. Stability profile of various formulations at 25 ± 1°, 37 ± 1° and 60± 1°.

Week	Percentage of potency at temperature		
	25 ± 1°	37 ± 1°	60± 1°
2	99.20	99.02	98.89
4	99.12	98.99	98.87
6	99.17	99.10	98.92
8	99.27	99.12	98.76
10	99.02	99.02	98.82
12	98.85	98.65	98.44
14	98.60	98.47	98.51

Figure-4. In vitro drug release kinetics of lamivudine floating alginate beads – Higuchi plot.
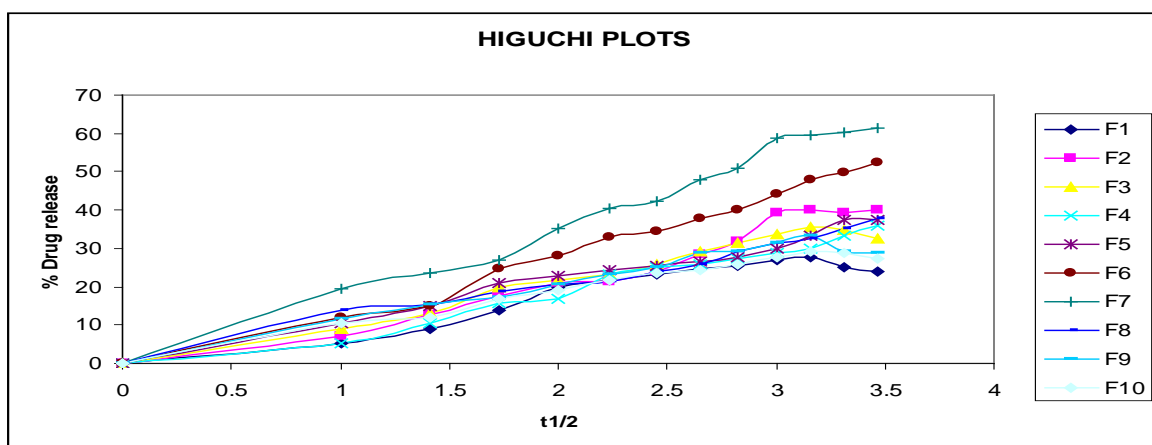
Figure-5. FTIR spectrum of powdered beads of F7 formulation
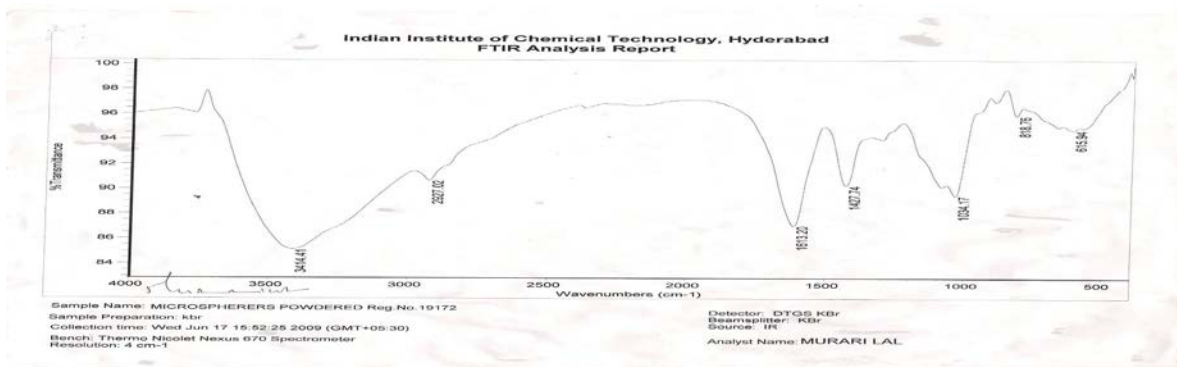

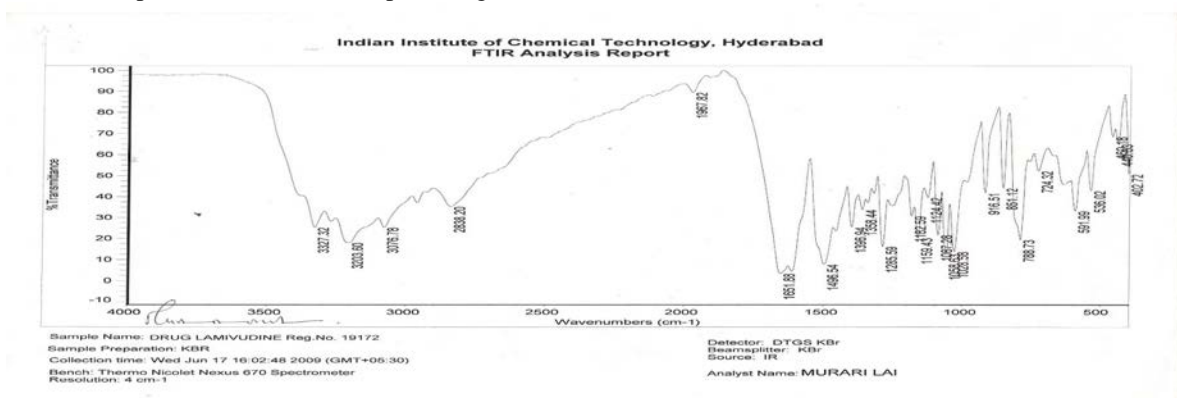
Figure-6. FTIR spectrum of lamivudine pure drug

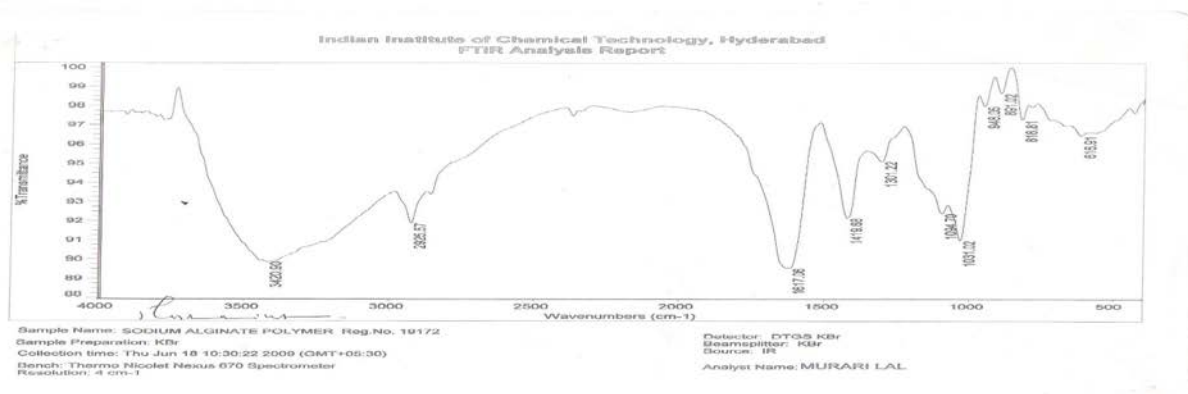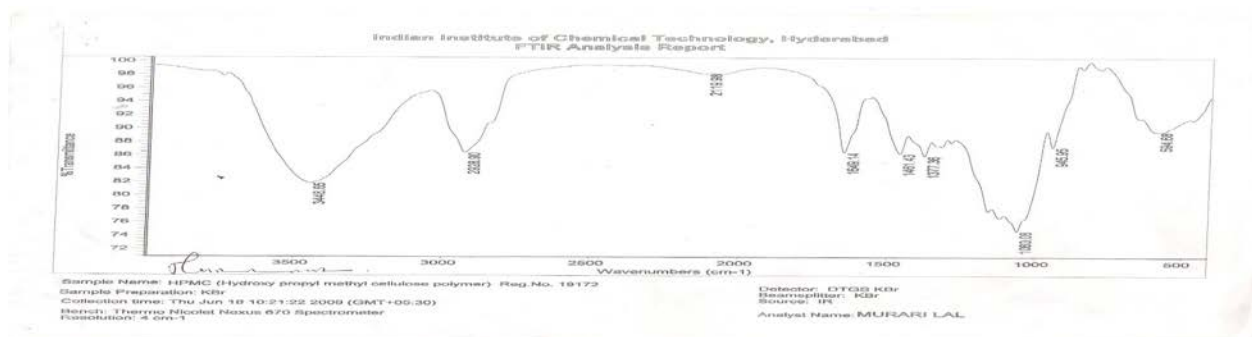Figure-7. FTIR spectrum of sodium alginate polymer

Figure-8. FTIR spectrum of HPMC polymer

Interpretation of data was based on the value of the resulting regression coefficients. The *in vitro* drug release showed the highest regression coefficient value for zero order models indicates diffusion to be the predominant mechanism of drug release. The drug release rate was following zero order kinetics (figure-3), which complies with the controlled delivery of lamivudine over 12 hours. Except F1, F2, F6, F7, F8 the other formulations followed Higuchi square root kinetic model indicating the diffusion controlled drug release(figure-4), which creates a restriction in optimizing the methods, as zero order model is the most desirable. F1, F2, F6, and F8 were rejected on the basis of particle size, yield factor, entrapment efficiency and prolongation of drug release in comparision with F7.

Floating behavior: The floating test was performed to investigate the floatability of the prepared microspheres. The microspheres floated for prolonged time over the surface of the dissolution medium. Good in vitro percentage buoyancy was observed for all the microsphere formulations. Buoyancy percentage of the microspheres was in the range 68.9± 0.7(F3) to 84.8±0.7 (F7) (Table-1). F7 formulation showed the best floating ability 84.8±0.7 (F7) as compared with other formulations.

Floating lag time: The floating lag time of all the formulations were measured. All the formulations could float to the top in less than 1 minute.

Accelerated stability studies: The accelerated stability studies were performed according to ICH guidelines for 14 weeks and the results were found to be stable as shown in Table 3.

FTIR studies: The interaction study between the drug (lamivudine) and polymers (HPMC, sodium alginate) in different formulations was evaluated using FTIR spectrophotometer. Four bands present in lamivudine spectrum due to the formation of N-H, O-H, C=O, C=N linkage respectively, was also detected and identified in the spectrum of the formulations, confirming no drug-polymer interaction as represented in Figure-(5,6,7 and 8). The FTIR study attests the safety profile of the microspheres due to avoidance of drug polymer interactions.

CONCLUSION

Floating alginate gel beads of lamivudine showed excellent floating ability, good buoyancy and prolonged drug release. Diffusion was found to be the main release mechanism. In context to the intense worldwide research to combat AIDS, it can be envisaged that future workers would indulge in optimization of the selected formulation (F7), to promote its commercial scale up leading to floating alginate gel beads of lamivudine for effective management of AIDS. These microspheres were capable of reducing the frequency of administration and dose dependent side effects associated with the repeated administration of conventional lamivudine Tablets.

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