RESEARCH ARTICLE

Design and Optimization of Lamivudine Floating Microspheres

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ABSTRACT

The present study was focused to develop floating microspheres of Lamivudine in order to achieve an extended retention in the upper gastrointestinal tract, which may result in enhanced absorption and thereby improved bioavailability. The present study involves preparation and evaluation of floating microspheres using Lamivudine as a model drug for prolongation of the gastric retention time. As Lamivudine is mainly absorbed from stomach, thus using floating microspheres as a mode of drug delivery helps in increasing its residence time and hence increasing the bioavailability of drug. The microspheres were prepared by the Ionic gelation method. The average diameter and surface morphology of the prepared microspheres were characterized by optical microscope and scanning electron microscopic methods respectively. The prepared microspheres were evaluated for particle size, micromeritic study, drug entrapment efficiency, *in vitro* buoyancy, swelling index and *in vitro* release. The effect of various formulation variables on the size and drug release was also investigated. All the formulated microspheres were found to possess good flow properties. Scanning electron microscopy confirmed spherical structure of the prepared microspheres. The best formulation F3 drug release kinetics were evaluated using Zero order, First order, Higuchi model, Korsmeyer - Peppas model. After the interpretation of data that was based on the value of a resulting regression coefficient, it was observed that the Korsmeyer-Peppas model has a highest regression coefficient values indicating that the drug release was based on the erosion of polymeric chain matrix system

Keywords: Lamuvudine, Floating microspheres, Gum acacia, Zero order, First order, Higuchi model, Korsmeyer-Peppas model

Introduction

Drug delivery through oral route is frequently used for delivery of drug due to ease of administration, patient compliance and flexibility in formulation. Gastric emptying is a highly variable process; different types of problems are faced in designing of controlled release systems. One of such problems is the inability to keep them in the desired area of the gastrointestinal tract.

Main problem with conventional drug delivery systems is to maintain the drug concentration within the therapeutically effective concentration level and the same being achieved only when taken several times a day. Success of an oral drug delivery system depends on its degree of absorption through gastrointestinal tract (GIT). Various methods have been designed to increase the gastric residence time (GRT) which include: floating drug dosage systems (FDDS), swelling or expanding systems, mucoadhesive systems, high-density systems, modified-shape systems and other delayed systems. On the basis of the mechanism of mucoadhesion, floatation and sedimentation, gastric retention of solid dosage forms may be achieved, which improves the absorption of drug. Such retention systems are important for the drugs that are degraded in intestine or for drugs like antacids or certain enzymes that should act locally in the stomach and also for the drugs that are poorly soluble in intestine due to alkaline pH, gastric retention may increase solubility and enhance absorption so resulting in improved bioavailability. Such system gives advantage in improving gastrointestinal absorption of drugs that have a narrow absorption window and also for drugs having site-specific absorption limitations (Dubey et al., 2012).

Hollow microspheres are considered as one of the most promising buoyant systems. They possess the unique advantages of multiple unit systems and in addition better floating properties. The general techniques involved in their preparation include emulsion solvent evaporation and emulsion solvent diffusion. The drug release and better floating properties mainly depend on the type of polymer, plasticizer and the solvent employed for the preparation.

The ability of polymer microspheres to deliver medication in a rate-controlled and sometimes targeted manner has been demonstrated over time. The mechanism of drug release from microspheres is by drug leaching from the polymer or by degradation of the polymer matrix. Since the rate of drug release is controlled by these two factors, it is important to understand the physical and

chemical properties of the releasing medium (Freiberg, 2004).

Of the many polymeric drug delivery systems, biodegradable polymers have been used widely as drug delivery systems because of their biocompatibility and biodegradability. The biodegradable polymers have the ability to release the drug in a controlled manner which has been extensively harnessed in the production of microparticles. The factors responsible for controlling the drug release rate from the microparticles thus formed include the physicochemical properties of drugs, degradation rate of polymers, and the morphology and size of microparticles (Park et al., 2005).

The use of natural polymers is encouraged by the fact that they contain reactive sites available for ligand conjugation, cross-linking, and other modifications which renders the polymer tailored for a range of clinical applications. Natural polymers also often possess good cytocompatibility, making them popular choices for tissue engineering scaffolding applications.

Gum acacia is also known by the name Gum Arabic. It is a good binding agent and is used in the preparation of lozenges, pastilles and compressed tablets. It is also used to form coacervates for microencapsulation of drugs (Kokate et al., 2010). Sodium bicarbonate is generally used in pharmaceutical formulations in preparation of effervescent tablets and granules. It is also used in tablet formulations to buffer drug molecules that are weak acids, thereby increasing the rate of tablet dissolution and reducing gastric irritation. Recently, sodium bicarbonate has been used as a gas-forming agent in alginate raft systems and in floating, controlled release oral dosage forms for drugs. Therapeutically, sodium bicarbonate may be used as an antacid. Sodium bicarbonate is used in food products as an alkali or as a leavening agent, e.g. baking soda (Rowe et al., 2009).

Sodium alginate or alginic acid is used in a variety of oral and topical pharmaceutical formulations. In tablet formulations, sodium alginate may be used as both a binder and disintegrant. Sodium alginate has also been used in the preparation of sustained-release oral formulations since it can delay the dissolution of a drug from tablets, capsules and aqueous suspensions. Therapeutically, sodium alginate has been used in combination with an H2-receptor antagonist in the management of gastroesophageal reflux and as a hemostatic agent in surgical dressings. Sponges composed of sodium alginate and chitosan are shown to produce sustained release systems (Rowe et al., 2009). Calcium carbonate is being mainly used as an

excipient. It has been used as an antimicrobial preservative, as a desiccant and as an astringent in eye lotions. Calcium is essential for the formation of skeletons, neural transmission, muscle contraction, and coagulation of the blood. Chloride ions are also required for normal cellular operations in animals and humans, and serve as a micronutrient for plants, playing important roles in photosynthesis and osmoregulation (Rowe et al., 2009).

Materials and methods

Materials: Lamivudine was obtained as a gift sample from East African Overseas Ltd., Dehradun. The organoleptic examination of drug revealed the drug was white in colour, bitter in taste and it has no odour. The drug was found to be soluble in Methanol, Ethanol, Chloroform, Methylene chloride, Isopropyl alcohol and insoluble in water. The drug melting was found to be 182-183ºC. Sodium alginate and Gum acacia was purchased from market of Khari Bauli, Delhi. All chemical and reagents used were of laboratory grade.

Methods: Floating microspheres were prepared by Ionotropic gelation method. Sodium alginate was dissolved in sufficient amount of water with maintaining the temperature between 40-50ºC. Then the required amount of polymer was added into it. When the polymer dissolved, drug was added into it and dispersed in the polymer solution. A 10% Calcium chloride solution was prepared as a continuous phase and placed it on the magnetic stirrer. The drug and polymer solution was filled into a syringe and dropwise added into the calcium chloride solution by using #24 gauge needle. $CaCl_2$ solution acts as a crosslinking agent and causes gelation of the poured droplets leading to formation of microspheres. The prepared floating microspheres were allowed to stand in the calcium chloride solution for 30 minutes for curation. After that the microspheres were filtered by using Whattman filter paper. The filtered microspheres were dried in a hot air oven at 50ºC temperature and stored. Composition of prepared floating microsphere was showed in table 1.

Calibration curve of Lamividine using UV spectroscopy

Preparation of 0.1N HCl

8.5 ml of HCl was dissolved in distilled water and volume was made up to 1000 ml to make 0.1N HCl.

Preparation of stock solution

10 mg of drug was taken and transferred to a 10 ml volumetric flask, and methanol was added and volume was made up to 10ml. Then 5, 7.5, 10, 12.5, and 15µg/ml concentration solutions were prepared

successively with the help of 0.1N HCl and scanned one of the solutions between 200-400 nm. The λ_{max} was found to be 270 nm and after that the absorption of prepared various concentration of drug solution was taken. The method obeys Beer's law in the concentration range of 5-15 µg/ml (Jamadar et al., 2011). Table 2 depicts the absorbance of various concentrations of the standard dilutions obtained.

Table 1: Composition of prepared floating microspheres of Lamivudine

Formulations	Drug (mg)	Gum acacia (mg)	Sodium alginate (mg)	Sodium bicarbonate (mg)	$CaCl_2$ (% Conc.)
F1	100	60	100	200	10
F2	100	80	100	200	10
F3	100	100	100	200	10
F4	100	125	100	200	10
F5	100	150	100	200	10
F6	100	180	100	200	10

Table 2: Absorbance of standard dilutions at 270 nm

S. No.	Concentration (µg/ml)	Absorbance
1	5	0.214
2	7.5	0.392
3	10	0.529
4	12.5	0.626
5	15	0.922

FT-IR spectroscopy of drug and polymer

FTIR Spectroscopy was used to check the compatibility between the drug and the excipients being used. The various peaks observed for the pure drug are represented below:

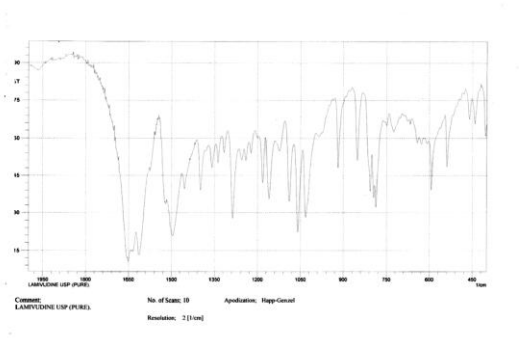

Fig. 3 IR Spectra of Lamivudine

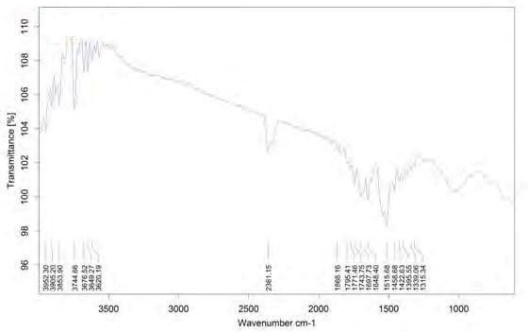

Fig. 4 IR Spectra of Gum acacia

Compatibility study

IR study was performed to study compatibility between drug and polymer. Drug and polymers were mixed in 1:1 ratio after that mixture was observed on FTIR spectroscopy.

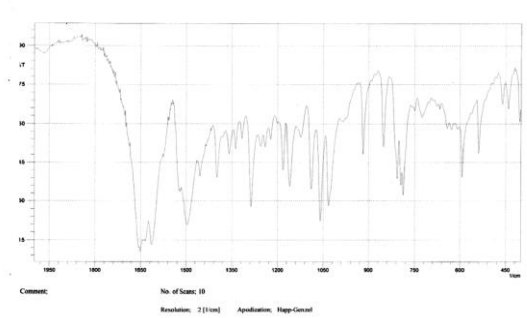

Fig. 5 IR Spectra of mixture of Lamivudine, Gum acacia and Sodium alginate

As the major peaks seen in the spectra of Lamivudine appear unaltered in the drug & excipient mixture, it was concluded no interactions occur between the drug and the polymer.

Characterization of floating microspheres

Shape and surface characterization

Prepared formulations were subjected to Scanning electron microscope (SEM) for surface study of floating microsphere. Surface morphology of microspheres was investigated by Scanning Electron Microscopy (SEM) using JSM 6380A (JOEL, Japan). The microspheres, coated with Platinum by ion sputtering using Auto fine coater JFC-1600 (JOEL, Japan), for 20 s at 1.1V under argon atmosphere were mounted onto metal stubs using double-sided carbon adhesive tape and the scanning electron micrographs were taken.

Percentage yield

The percentage yield of the floating microspheres is determined for drug and is calculated by using the following Eq. 1 (Punitha et al., 2010).

% yield = total weight of floating microsphere/total weight of drug and polymer Eq. (1)

Particle size

The particle size of the microspheres is measured using optical microscopic method (Hicon, Delhi) and the mean particle size is calculated by measuring 50 particles with the help of a calibrated ocular micrometre (Gangadharappa et al., 2011). Least count of the instrument was found to be 0.01mm.

(Stage reading)/(Occular reading) × 100

Eq. (2)

Bulk density

It is the ratio of mass of the blend to bulk volume. It is measured by pouring powder in measuring cylinder and measuring the volume occupied by powder and is calculated by following Eq. 3 (Aulton, 2002)

Bulk Density = Mass/Bulk volume Eq. (3)

Tapped density

It is the ratio of mass of the blend to tapped volume. It is measured by digital tap densitometer by measuring the volume occupied by powder after 100 standard

tapping and it is calculated by following Eq. 4.

Tapped Density = Mass/Tapped Volume Eq. (4)

Carr's (compressibility) index

Compressibility index (C.I.) or Carr's index value of micro particles is calculated according to the following Eq. 5 (Trivedi et al., 2008).

% compressibility = Tapped density – Bulk density× 100/Tapped density Eq. (5)

The value given below 15% indicates a powder with usually give rise to good flow characteristics, whereas above 25% indicate poor flow ability.

Hausner ratio

It is calculated by following Eq. 6 (Trivedi et al., 2008).

% compressibility = Tapped density/Bulk density Eq. (6)

If value of it is less than 1.25, it denotes good flow properties and if the value is greater than 1.25, it denotes poor flow.

Angle of repose

Angle of repose (θ) of the microspheres is measured using funnel method. This method is preferred because it is most closely mimic the manufacturing situation in industry in which powder in motion The microspheres is poured through a funnel that can be raised vertically until apex of pile touches the lower tip of the funnel . The radius and angle of repose is obtained by Eq. 7.

$\tan \theta = h/r$ Eq. (7)

Where, θ = Angle of repose; h = Height of the pile; r = radius of the circle covered by heap on the graph paper.

Swelling Index

Firstly we were prepared 0.1N HCl maintained its pH -1.2. Then we were taken a petridish and transfer the specific amount of floating microspheres, added a 0.1 N HCl. The floating microspheres were taken out from the HCl and soak the extra water with the help of tissue paper. Then weight them and it was calculated by using the following formula:

Swelling Index = [(Mass of swollen microspheres - Mass of dried microspheres) / Mass of dried microspheres] * 100

Water uptake ratio

Water uptake in this case was presented as normalized weight gain ratio as defined below:

$Y = m_W/m_d$ Eq. (9)

Where,

Y is the normalized weight gain ratio, m_W the microspheres weight after swelling (including water uptake), and m_d is the initial dry microspheres weight.(Pande et al., 2010)

Floating Time

The floating microspheres were placed in the 500 ml of 0.1N HCl and examined for the duration of time till they float.

Drug entrapment efficiency

Firstly crush the floating microsphere and transferred into volumetric flask that contain 0.1N HCl and the volume was made up using 0.1N HCl. The solution was filtered and after that absorbance was measured by UV spectrophotometer and the amount of drug entrapped in the microspheres was calculated by the following Eq. 10 (Tang et al., 2007).

% Entrapment efficiency = (Amount acually present)/(Theoretical drug content)× 100 Eq. (10)

Scanning electron microscopy

Surface and cross-sectional morphologies of beads were examined with a Scanning Electron Microscope (SEM Leo 430, England). Beads were mounted on metal grids using double- sided tape and gold coated under vacuum.

***In- vitro* buoyancy**

The floatation studies were carried out to ascertain the floating behaviour of the prepared formulations. Beaker method was initially used to have an idea of the floatation behaviour of the proposed dosage form. 50 mg of floating microparticles were placed in each of four 50 ml beakers containing 20 ml of 0.1N HCl containing 0.02% tween 80. The beakers were shaken in a biological shaker at 37ºC ± 0.5ºC at40 r.p.m. Floating microspheres were collected at 4,8 and 12 hrs and dried till constant weight was obtained. The percentage of floating microspheres was calculated by the following Eq. 11 (Wilding et al., 1994).

% Buoyancy = [Weight of floating microspheres/ Initial weight of microspheres] * 100

Table 3 Micromeritic properties of prepared formulations

Formulation	Bulk density	Tapped density	Angle of Repose	Carr'a Index	Hausner Index
F1	0.96	0.99	14	0.04	0.97
F2	0.81	0.88	16.1	0.10	0.90
F3	0.35	0.44	16	0.14	0.85
F4	0.41	0.51	12	0.23	0.70
F5	0.75	0.82	19.1	0.07	0.92
F6	0.54	0.63	14	0.19	0.87

Table 4 Characterization of floating microspheres

Formulation	Particle size	Entrapment efficiency	Buoyancy	Yield (%)	Water gain
F1	828.52 ±10.60	67.84	68.13	93.4	1.4
F2	834.02 ±7.96	70.23	69.34	91.9	1.3

F3	839.60 ±7.11	78.29	85.42	96.0	2.4
F4	866.74 ±12.11	83.51	75.48	78.2	1.5
F5	874.36 ±8.81	85.22	71.33	56.7	1.5
F6	1140.86 ±8.05	86.37	70.46	51.9	1.5

In-vitro release study

An accurately weighed amount of drug loaded floating microspheres equivalent to 50 mg of cephalexin were subjected to *in vitro* release studies using USP type II apparatus placed in 500 ml of 0.1N HCl, temperature was maintained at 37ºC and sampling was done at 5, 10, 15, 30, 60, 90, 120, 180, 240, 360, 480,1440 minute time interval and take the absorbance under the UV spectroscopy at 229 nm During dissolution 5 ml aliquots were withdrawn at different time intervals of 1 to 24 h and same was replaced with equal volume of fresh medium (Swarnkar et al., 2012).

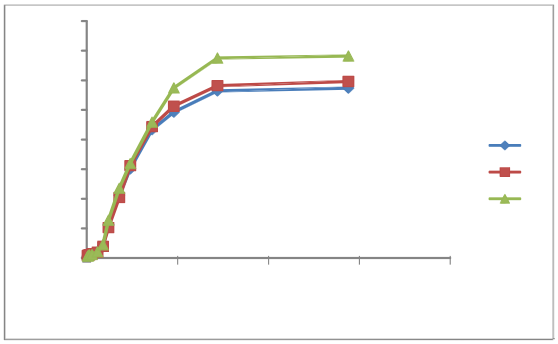

Fig. 11 % Release of drug (F1-F3)

Table 5 In vitro drug release from different formulations at different time intervals

Time (min)	% release of drug					
	F1	F2	F3	F4	F5	F6
5	0.74	0.84	0.67	1.16	1.54	1.8
10	0.79	0.95	0.72	1.98	2.03	2.15
15	0.84	1.03	1.12	2.01	2.57	2.78
30	1.08	1.42	1.22	2.94	4.81	3.07
60	2.07	1.98	2.08	4.98	5.02	5.97
90	4.21	3.92	4.49	6.92	6.54	6.72
120	11.2	10.23	12.76	15.94	16.32	17.35
180	21.2	20.43	23.56	28.26	30.25	32.61
240	30.07	31.16	31.92	34.57	36.24	40.24
360	43.31	44.38	45.89	47.64	48.3	51.23
480	49.23	51.27	57.43	60.17	62.50	64.32
720	56.40	58.20	67.50	72.80	74.30	75.60
1140	57.36	59.64	68.30	74.52	78.20	77.74

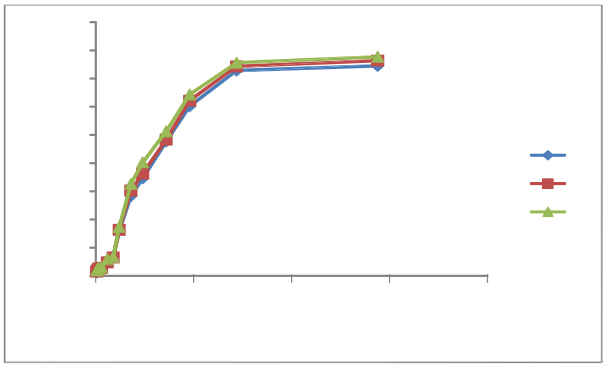

Fig. 12 % Release of drug (F4-F6)

Release kinetics

The drug release parameters for the optimized formulation i.e. F3 were fitted to various release models. After that we found that the kinetics of drug release from

the prepared formulations F3 follows Korsmeyer – Peppas model as represented in Fig. 14.

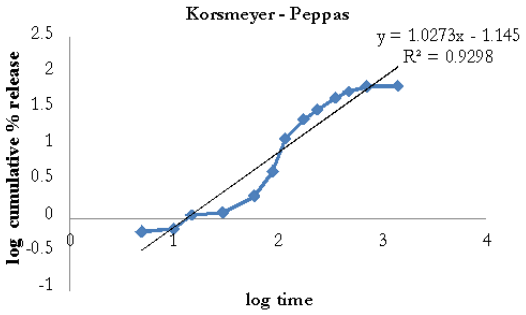

Fig. 14 Log cumulative % release with log time (F3)

Table 6 Regression coefficients using different release models

Formulation	Regression coefficients (r^2) derived from release data for formulation (F3) using different drug release models			
	Higuchi	Korsmeyer-Peppas	First order	Zero order
F3	0.9048	0.9298	0.5112	0.7495

Results and Discussion

The prepared floating microspheres were found to be spherical in nature and white in colour. On SEM analysis, it was observed that the surface of the floating microspheres was rough and bearing small pores. Some of the pores are bigger in size and some were very small. The pores were formed as a result of defects in crosslinking. It was observed that drug release occurs due to these pores formed on the surface of microspheres.

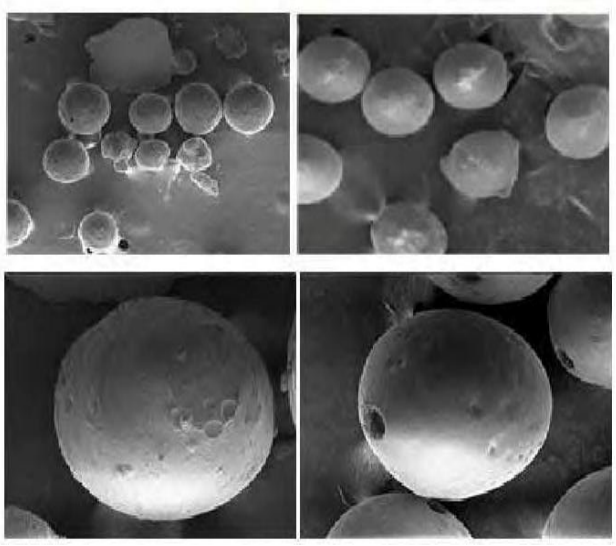

Fig. 15 SEM of microspheres

The average particle size of the different microsphere formulations is depicted in Table 6. The trend depicted is that the formulation F6 has the biggest particle size with others having little difference in their size ranges with F1 having the smallest microspheres.The increase in particle size with increase in polymer concentration may be attributed to the fact that the viscosity of the polymer solution increases with increasing polymer concentration, which in turn decreases the stirring efficiency. It was found that average percentage yield was

greater than 50 % for all the batches which shows the suitability of this method for preparation of microspheres. The maximum percentage yield was found of F3 formulation and was noted to be 96%. It was observed that the yield increases as the concentration of gum acacia is increased over F1-F3 and the yield was highest in case of F3 formulation. However the percentage yield decreases on moving from F3-F6 when the concentration of the polymer is further increased.

All the formulations prepared i.e. F1-F6 exhibited good flow behaviour. The Carr's compressibility index was found for F1 to F6 in the range of 0.03- 0.23. The Carr index is an indication of the compressibility of a powder. The smaller the Carr's Index the better the flow properties. A Carr index greater than 25 is considered to be an indication of poor flowability, and below 15, of good flowability. Thus the value of Carr's index for all the formulations depicts that they have good flow properties. Hausner's ratio was found for F1 to F6 in the range of 0.70 – 0.96. The value of Hausner's ratio greater than 1.25 is indicative of poor flowability, and as all the formulations have their values below 1.25.

With the increase in polymer concentration, increased entrapment efficiency was seen probably because with increasing polymer content, more particles of Lamivudine would be coated leading to higher encapsulation efficiency as can be seen from Table 6. The results show that gum acacia containing microspheres showed a desirable high drug content and entrapment efficiency. Many factors affect the entrapment efficiency of the drug in microspheres e.g. nature of the drug, polymer concentration, drug-polymer ratio and stirring speed etc. Generally low concentration of polymer shows low encapsulation efficiency. However the drug loading was found to decrease with increase in the polymer concentration due to its higher viscosity which affects the diffusion coefficient of drug. Drug entrapment was attributed to the permeation characteristics of polymers used, that could facilitate the diffusion of part of entrapped drug to the surrounding medium during preparation of floating microspheres.

Table 7 Swelling index of different formulation

Time (min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
30	10	0	20	20	10	12
60	20	10	35	30	20	25
120	40	30	44	42	38	40
240	30	50	61	58	53	57
360	10	65	79	70	71	68

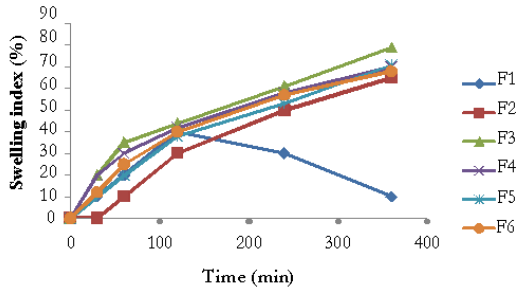

Fig. 9 Swelling index of various formulations

From the above data it can be seen that the formulations show swelling index in respective order: F3<F4<F5<F6<F2<F1. From **Figure 9**, it is observed that the formulation F3 possesses highest swelling index and F1 has the lowest swelling index. As a general trend it was observed that as the concentration of gum acacia increases, swelling was found to increase. However after a certain point it was seen that the swelling decreases, this may be due to the fact that with increase in polymer concentration instantaneous gelation occurs, which may lead to formation of a non penetrable layer which stops any further swelling by stopping water uptake.

In vitro buoyancy studies revealed that in spite of stirring the dissolution medium for more than 12 hours about 68 to 85% microspheres of batches F1 to F6 still continued to float without any apparent gelation. The absence of the floatation lag time for all the formulations indicates that the original density of the microcapsules prior to matrix swelling in simulated biofluids was less than 1. This indicates that the microspheres exhibit good buoyancy which may be attributed to the pores and cavities present in them and also to the fact all the formulations have a density less than gastric fluid 1.004 g/cm^3. Formulation F1 showed least percentage buoyancy of 68.13 %, while F3 showed highest buoyancy of 85.42 %. The formulations prepared with the various drug and polymer ratios were evaluated for floating time. All the formulations were found to float over 0.1 N HCl up to 24 hours.

It was found that with an increase in the concentration of Gum acacia polymer there was a decrease in the release rate of the drug upto certain extent however as the concentration of acacia exceeds a certain limit there was a contraindicatory increase in drug release. It may be due to the fact that as the polymer concentration increased the coacervation of the microspheres occurred too rapidly because of instantaneous crosslinking leading to the formation of irregular microspheres with bigger pore sizes which are not that effective in controlling the rate of drug release. It can thus be concluded from the above observations that the floating microspheres of F3 formulation are

able to release the drug in sustained and prolonged release manner in the GIT fluids. It was found that more than 55 % of entrapped drug was released in 24 hours. The optimized formulation F3 released the drug at the end of 24 hours was 68.2%.

The data obtained for the *in vitro* release of optimized formulation F3 were fitted into equations for the zero order, first order, and Higuchi release models, Korsmeyer- Peppas model. The interpretation of data was based on the value of a resulting regression coefficient. The in vitro drug release showed the highest regression coefficient values (r^2=0.9298) for Korsmeyer- Peppas model, indicating erosion of polymeric chain as the mechanism of drug release.

Conclusion

Floating microspheres of Lamivudine were prepared by the ionotropic gelation technique. Lamivudine is insoluble in water but soluble in organic solvent: ethyl alcohol, methylene chloride, chloroform and methanol. The absolute bioavailability of Lamivudine is 98%. It is less soluble in water, hence such a drug requires a novel gastroretentive drug delivery system which can provide an extended period of time in stomach and improve oral bioavailability. Hollow microspheres are suitable for drug delivery system of the drugs that have poor solubility in water. Hollow microspheres were formed by ionotropic gelation method. In the preparation of floating microspheres gum acacia, sodium alginate and sodium bicarbonate was used. Gum acacia was used for controlling release of drug. Sodium bicarbonate was used for keeping the microspheres floating. Sodium alginate was used for microencapsulation of drug. Floating microspheres were studied for characterization, compatibility study, particle size and shape, in vitro drug release, entrapment efficiency and buoyancy time. After the investigation of all formulations it was found that formulation F3 was an optimized formulation. Thus, prepared floating hollow microspheres of Lamivudine may prove to be potential candidates for a multiple-unit drug delivery device adaptable for any intragastric condition.

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