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Development And Evaluation of Gastroprotective Mucoadhesive Microspheres for Treatment of Epilepsy

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KEYWORDS

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ABSTRACT:

Oral drug delivery systems face challenges such as low bioavailability due to the heterogeneity of the gastrointestinal system, pH of the commensally flora, gastric retention time of the dosage form, surface area, and enzymatic activity. Conventional drug delivery systems may not overcome the issues imposed by the gastrointestinal tract (GIT) such as incomplete release of drugs, decrease in dose effectiveness, and frequent dose requirement. Therefore, the failure of conventional drug delivery systems to retain drugs in the stomach may lead to the development of gastro retentive drug delivery systems. The formulation of lamotrigine microsphere, with mucoadhesive properties, was successfully developed by ionic gelation method. Mucoadhesive microspheres were prepared by simple emulsification phase separation technique. Chitosan mucoadhesive microspheres are known to swell in aqueous environments, due to hydration. As a new polymeric structure is formed by introducing bridges between polymeric chains during the cross-linking procedure, Such a structure can be characterized by lower and slower penetration of the solvent through the chain structure of the polymer, suggesting that the swelling ratio and hence the drug release characteristics of the microsphere can be controlled by varying the content of the cross-linking agent used during the manufacturing process.

Introduction:

Epilepsy is a disorder of the brain characterised by an enduring predisposition to generate epileptic seizures and by neurobiologic, cognitive, psychological and social consequences of this condition [1]. The epilepsy associated seizures are distinct to a person and undetectable sometimes and thus require special attention. Seizure is an event of transient occurrence of signs or symptoms due to abnormal, excessive or synchronous neuronal activity of the brain which can vary from short to long periods of vigorous shaking [2]. A “seizure” is a paroxysmal alteration of neurologic function caused by the excessive, hypersynchronous discharge of neurons in the brain. “Epileptic seizure” is used to distinguish a seizure caused by abnormal neuronal firing from a nonepileptic event, such as a psychogenic seizure. “Epilepsy” is the condition of recurrent, unprovoked seizures [3]. Epilepsy has numerous causes, each reflecting underlying brain dysfunction. A seizure provoked by a reversible insult (e.g., fever, hypoglycemia) does not fall under the definition of epilepsy because it is a short-lived secondary condition, not a chronic state. “Epilepsy syndrome” refers to a group of clinical characteristics that consistently occur together, with similar seizure type(s), age of onset, EEG findings, triggering factors, genetics, natural history, prognosis, and response to antiepileptic drugs (AEDs). The nonspecific term “seizure disorder” should be avoided [4]. The most recent International League Against Epilepsy (ILAE) classification of epileptic seizures and epilepsies (epilepsy syndromes), published in 2010, revises past classifications using terminology and concepts appropriate for the modern era [5]. Seizures are divided into three categories: generalized, focal (formerly called partial), and epileptic spasms. Focal seizures originate

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in neuronal networks limited to part of one cerebral hemisphere. Generalized seizures begin in bilateral distributed neuronal networks. A seizure can begin focally and later generalize. Seizures can originate in the cortex or in subcortical structures. Using a detailed history, EEG findings, and ancillary information, a physician can often categorize the seizure/epilepsy type, after which an appropriate diagnostic evaluation and treatment plan is formulated [6]. Floating drug delivery systems (FDDS) have a bulk density less than gastric fluid and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of the drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration [7]. Bio adhesive drug delivery systems (BDDS) are used as a delivery device within the lumen to enhance drug absorption in a site-specific manner. This approach involves the use of bio adhesive polymers, which can adhere to the epithelial cell surface or mucin in the stomach. It increases the GRT by increasing the intimacy and duration of contact between the dosage form and the biological membrane [8]. The adherence to the gastric wall increases residence time at a particular site, thereby improving bioavailability. Gastric mucoadhesion does not tend to be strong enough to impart to dosage forms the ability to resist the strong propulsion forces of the stomach wall [9]. The continuous production of mucous by the gastric mucosa to replace the mucous that is lost through peristaltic contractions and the dilution of the stomach content also seem to limit the potential of mucoadhesion as a gastro retentive force. Some of the most promising excipients that have been used are polycarbophil, carbopol, lections, chitosan and gliadin, etc. BDDS are used as a delivery device within the human to enhance drug absorption in a site-specific manner [10]**.** Gastro retentive drug delivery system release dosage forms have been demonstrated to improve therapeutic efficiency by maintenance of a steady drug plasma concentration. Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. In addition, Gastro retentive drug delivery systems can enhance the controlled delivery of drugs by continuously releasing the drug for an extended period at the desired rate and to the desired absorption site until the drug is completely released from the dosage form [11]. Lamotrigine, an antiepileptic agent, belonging to phenyltriazine class, is used as a monotherapy and as an adjunct with other antiepileptic agents for the treatment of partial seizures and primary and secondary generalized tonic – clonic seizures. The drug is unstable in the alkaline pH of the small intestine and has absorption window in the stomach. Hence, FDDS of Lamotrigine able to solve the problem of alkaline instability in stomach.

Material And Methods

Determination of absorption maxima (λ_{max}): The absorption maxima of drug (Lamotrigine) will be determined by scanning drug solution in double beam ultraviolet spectrophotometer between 200 to 400 nm wavelengths at dissolution medium (phosphate buffer pH 1.2; 0.1 N HCl) solution. Accurately weighed required quantity of drug 50 mg (Lamotrigine) was dissolved in 50 ml of dissolution medium containing Phosphate buffer pH 7.4 in 50 ml volumetric flask with the help of sonication in bath sonicator for 20 min to obtain 1000 µg/ml solution. From resulting solution take 1 ml and was diluted up to 100 ml with Phosphate buffer pH 1.2 or 0.1 N HCl solvent separately with sonication for 20 min to get 10 µg / ml solution with the help of methanol in 10 ml volumetric flasks. The spectrum of these solutions was run in 200 – 400 nm range in double beam UV spectrophotometer (Shimadzu, UV-1800, Shimadzu Corporation, Kyoto, Japan) [12].

Preparation of calibration curve of Lamotrigine: Accurately weighed required quantity of drug 50 mg (Lamotrigine) was dissolved in 50 ml of dissolution medium containing Phosphate buffer pH 1.2 or 0.1 N HCl in 50 ml volumetric flask with the help of sonication in bath sonicator for 20 min to obtain 1000 µg/ml solution. From resulting solution take 10 ml and was diluted up to 100 ml with Phosphate buffer pH 1.2 or 0.1 N HCl solvent separately with sonication for 20 min to get 100 µg / ml solution. From above prepared resulting solution of 100 µg / ml, withdrawn 0.5 ml, 1.0

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ml, 1.5 ml upto 4.0 ml aliquots and diluted up to 10 ml with respective solvent (Phosphate buffer pH 7.4) in 10 ml volumetric flasks to get concentration of 5 µg / ml, 10 µg / ml, 15 µg / ml, upto 40 µg / ml respectively. The absorbance of each solution was measured separately at 271 nm for Phosphate buffer pH 1.2 or 0.1 N HCl. The absorbance was measured and standard curve was plotted between absorbance vs. concentration [13].

Preformulation study:

Organoleptic properties*:* The organoleptic properties of drug such as color, odor and taste will be noted visually.

Microscopic examination: The microscopic examination of the drug sample was done to identify the nature / texture of the powder. The required amount of powder will spread on a glass slide and examine under phase contrast microscope and drug powder was crystalline in nature.

Physical Characteristics*:*

i. Density: The drug powder will be weighed accurately and kept through a glass funnel into graduated cylinder. During this experiment the volume will note and bulk density will be determined. The tapped density will determine using tapped density apparatus. Bulk and tapped densities of Lamotrigine was to be 0.881 gm / cm^3 and 0.921gm / cm^3.

ii. Particle size: The average particle size (d_{avg}) of drug will be determined by means of optical microscope fitted with ocular micrometer and stage micrometer. The particle size of unmilled Lamotrigine was to be 29.7 µm

iii. Flow properties: The flow properties of drug powder were characterized in terms of carr's index, hausner's ratio and angle of repose. The Carr's index ((I_C)) and Hausner's ratio (H_R) of drug powders were calculating according to following equation:

Carr's Index (I_C) = $\rho_{Tapped} - \rho_{Bulk} / \rho_{Tapped}$

Hausner's ratio (H_R) = $\rho_{Tapped} / \rho_{Bulk}$

The angle of repose (θ) was measured by fixed height method. This was calculated by following equation:

Angle of repose (θ) = $\tan^{-1}$ 2 H / D

Where H is the surface area of the free standing height of the powder pile and D is diameter of pile that formed after powder flow from the glass funnel.

Solubility determination: Saturation solubility of of drug API (Lamotrigine) was determined by incremental method analysis method in various solvents. The exact quantity of drug 50 mg was placed on the conical flask and the various solvents i.e. distilled water, 0.1 N HCl, Phosphate buffer pH 6.8 and pH 7.4 phosphate buffers separately filled in burette. The solvent was slowly added into drug containing conical flask until the drug was solubilized and stirred constantly overnight at 37±0.5ºC. The samples were filtered by using Whatmann filter paper (0.45µm pore size). The solubility assessment of drug was determined by calculation of concentration µg/ml unit.

Partition coefficient: The partition coefficient of drug samples was observed in mixed solvent of 100 ml containing n-octanol: phosphate buffer pH 7.4. 100 mg of drug was added into 50 ml each of an n-octanol and buffer phase in a separating funnel. The mixture was shaken for 24 h until equilibrium reached. Both medium were divided and collected individually, filtered. The quantity of API dissolved in aqueous medium was diluted and determined by UV spectrophotometric method. The partition coefficient of API was calculated from the proportion between the concentrations of drug in organic and buffer solution quantity using following equation.

Log $P_{(oct / pH\ 7.4)}$ = Log (C_{noct} – $C_{pH7.4}$) equilibrium

Melting point: The melting point of drug samples were obtained by pinch of drug material sample filled in capillary tube by manually. Capillary tube sealed from one end with a bunsen flame burner individually. The filled capillary tube was kept in melting point apparatus and identified the temperature at which the drug was starting to melt.

Drug excipient compatibility study:

Infrared spectroscopy of drugs: The functional group determination of drug samples was identified by IR spectroscopy. Infra-red spectroscopy was carried out by using Shimadzu IR Spectra photometer as method given below. The characteristic peaks were reported as wave number. The FTIR spectra of dried drug samples (Lamotrigine) independently were obtain by FTIR

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spectrophotometer by means of the potassium bromide disc method. The drug sample was pulverized and thoroughly mixed with a dried powder of IR grade potassium bromide material with weight ratio of 3:1 (i.e 9 mg of KBr in 1 mg of drug). The mixture of materials was pressed using a hydrostatic press at a pressure of 10 tons for 5 min at room temperature with required humidity. The disc of sample was placed in the sample holder for measuring the spectrum and the spectra were recorded as the wave number ranges 4000-400/cm at a resolution of 4/cm. The compatibility i.e. drug-excipients interaction studies are helpful for dosage form design. For compatibility studies drug / excipients ratio are selected and investigated based on the reasonable drug / excipient ratio in the final product. Drug and other Excipients were weighed as 1:1 ratio and passed through sieve # 40, mixed well. The blend was filled in amber color glass vials and stopped with grey rubber stoppers followed by aluminium seal. The FTIR spectrum for Lamotrigine (recorded from a KBr pellet) is illustrated in Fig. 5.4. Characteristic infrared (IR) absorption bands due to amine N - H stretching (3450, 3314, 3212 cm^{-1}), aromatic (C = C) stretching (1619cm^{-1}), and ortho-distributed aryl C - Cl stretching (1052cm^{-1}) were observed.

Preparation method of mucoadhesive microspheres: Mucoadhesive microspheres were prepared by simple emulsification phase separation technique reported by Patel et. al. with slight modifications. The mucoadhesive microspheres were developed in different batches M1 to M5 as shown in Table 5.2. lamotrigine (50 mg) was dispersed in 1% w/v chitosan solution. The resultant mixture was extruded through syringe (No. 20) to 100 ml liquid paraffin (1:1 ratio of heavy and light) containing 0.2% Dioctyl sodium sulfosuccinate under stirring at 900-1200 rpm. After 15 minutes, crosslinked by glutaraldehyde 3ml (25% aqueous solution) and crosslinking time kept for 1 hour. Microspheres were filtered, washed with petroleum ether and water and allowed to air dry at room temperature for 24 hours [14].

Table 5.2: Batch specifications for mucoadhesive microspheres

S. No	Batch	Polymer	Drug polymer ratio (mg)	Stirring Rate (RPM)
1	M-1	Chitosan	01:01	900
2	M-2	Chitosan	01:02	900
3	M-3	Chitosan	01:03	900
4	M-4	Chitosan	02:01	900
5	M-5	Chitosan	03:01	900

Characterization of Mucoadhesive Microspheres

Particle size analysis: The size of mucoadhesive microspheres was determined by using an optical microscope (BEM-21, Besto Microscope, India) fitted with an ocular micrometer and a stage micrometer. The mean particle size was calculated by measuring 200-300 particles.

Micromeritic properties: The prepared mucoadhesive microspheres were characterized for their micromeritic properties such as true density, tapped density, % compressibility index and angle of repose. The tapping method was used to calculate tapped densities and % compressibility index

Yield of Microspheres: The prepared mucoadhesive microspheres were collected and weighed. The actual weight of obtained microspheres divided by the total amount of all non-volatile material that was used for the preparation of the microspheres **(Patel et al., 2006)**

$$\% \text{ Yield} = \frac{\text{Actual weight of the product}}{\text{Total weight of the excipients and drug}} \times 100$$

Incorporation efficiency: To determine the incorporation efficiency 100 mg mucoadhesive microspheres were taken and dissolved in 20 ml of 0.1N HCl. The solution was filtered to separate shell fragments. The estimation of drug was carried out at the λ_{max} of 271 nm by using a double beam ultraviolet

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spectrophotometer. The incorporation efficiency was calculated using following equation.

Swelling Index: The swelling characteristics of mucoadhesive microspheres were resolved correctly in the 0.1 N HCl (pH 1.2). Microspheres of known weight (50 mg) from different batches were placed in the dissolution medium (0.1 N HCl pH 1.2) for 24 hours and swollen microspheres were accumulated in a centrifuge. The swollen microsphere weight or mass was found out by first blotting the microsphere with filter paper to eradicate water which is absorbed on surface and after that undergone taking weight instantly in an electric balance. The percentage of swelling of microspheres in the dissolution media was then calculated by the formula contained in equation

$$\text{Swelling Index (Sw)} = \frac{W_t - W_0}{W_0} * 100$$

where, Sw =Percentage of swelling microsphere, W_t =Weight of microsphere at time 't' and W_o=Initial weight of the microspheres

Mucoadhesion Studies: The mucoadhesive characteristics of microspheres were determined by percentage mucoadhesion. A strip of rat stomach mucosa 1 cm × 1 cm was mounted on a glass slide and accurately weighed microspheres were placed on the tissue, kept in a desiccator at 90% relative humidity for 15 min to allow the microspheres to interact with the membrane and by fixing at an angle of 45^0 relative to the horizontal plane. Simulated Gastric Fluid (pH 1.2) was peristaltically pumped at a rate of 2 ml/min over the tissue. The washings were filtered and dried. The test was performed at stomach pH (0.1 N HCl, pH 1.2). Percentage of mucoadhesion was determined from the formula.

$$\% \text{ Mucoadhesion} = \frac{W_0 - W_t}{W_0} * 100$$

Where, W_o = weight of microspheres applied, W_t = weight of microspheres leached out.

***in-vitro* drug release:** in-vitro drug release studies were performed in 0.1 N HCl (pH 1.2) for all type of prepared microspheres i.e. mucoadhesive microspheres. The *in-vitro* release of lamotrigine from the different formulation of floating hollow microspheres was determined in 900 ml 0.1 N HCl at 100 rpm by using USP XXIII dissolution apparatus (paddle type). A weighed amount of floating hollow microspheres equivalent to 20 mg drug was placed in a non-reacting muslin cloth having a smaller mesh size than the microspheres. The mesh was tied with a nylon thread to avoid the escape of any microspheres and a glass bead was placed in the mesh to induce sinking of microspheres in the dissolution medium. The temperature of dissolution medium was maintained at 37 ± 0.5^0C. At specified time intervals, 5 ml aliquots were withdrawn, filtered, diluted with the same medium and assayed at 271 nm for lamotrigine using a double beam ultraviolet spectrophotometer (Labindia model-3000+ series). Samples withdrawn were replaced with equal volume of the same dissolution medium [15].

Results And Discussion

Analytical Study: The absorption maxima of drug (lamotrigine) will be determined by scanning drug solution in double beam ultraviolet spectrophotometer between 200 to 400 nm wavelengths at dissolution medium (phosphate buffer pH 1.2 or 0.1 N HCl) solution. Accurately weighed required quantity of drug 50 mg (Lamotrigine) was dissolved in 50 ml of dissolution medium containing Phosphate buffer pH 1.2 or 0.1 N HCl in 50 ml volumetric flask with the help of sonication in bath sonicator for 20 min to obtain 1000 µg/ml solution. From resulting solution take 1 ml and was diluted up to 100 ml with Phosphate buffer pH 1.2 or 0.1 N HCl solvent separately with sonication for 20 min to get 10 µg / ml solution with the help of methanol in 10 ml volumetric flasks. The spectrum of these solutions was run in 200 – 400 nm range in double beam UV spectrophotometer (Shimadzu, UV-1800, Shimadzu Corporation, Kyoto, Japan). The absorbance of each solution was measured separately at 271 nm for Phosphate buffer pH 7.4. The absorbance was measured and standard curve was plotted between absorbance vs. concentration.

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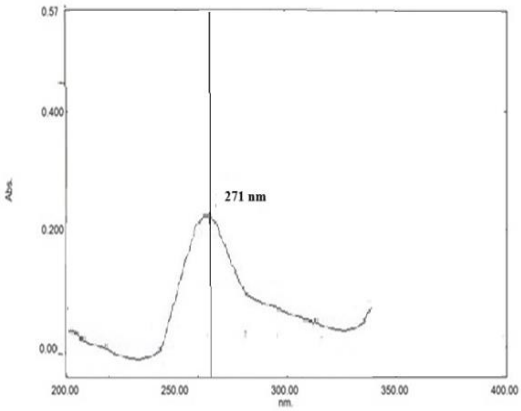

Figure 1: Absorption maxima (λ-max) of lamotrigine in phosphate buffer pH 1.2 or 0.1 N HCl solution (10 µg/ml)

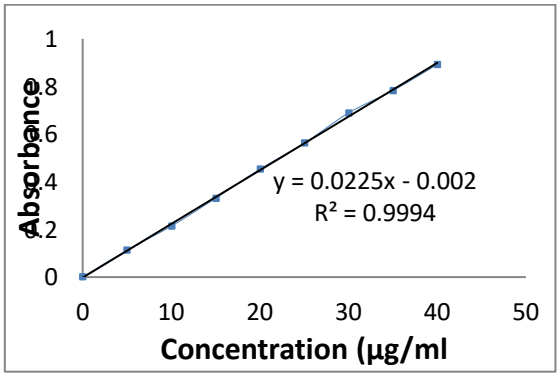

Figure 2: Standard curve of lamotrigine in phosphate buffer pH 1.2 or 0.1 N HCl (271 nm)

Characterization of Mucoadhesive Microspheres: The formulations of lamotrigine loaded mucoadhesive microspheres were developed by simple emulsification phase separation technique. Chitosan was selected as a polymer for the preparation of mucoadhesive microspheres owing to its biodegradable and mucoadhesive properties. In this method the drug-polymeric suspension was introduced into liquid paraffin with stirring from bottom side to reduce the aggregation of polymer on the top of liquid paraffin. This technique resulted more spherical microspheres and good yield of product could be achieved. In this formulation, chitosan was used as polymeric carrier in different ratio and mixture was extruded through syringe to liquid paraffin containing Dioctyl sodium sulfosuccinate under stirring, crosslinked by glutaraldehyde. Nine formulations were developed for characterization of mucoadhesive microspheres. SEM photo micrograph confirmed that prepared mucoadhesive microspheres were spherical with smooth perforated surface showed in batch M-5. The increase in polymer amount showed increase in microsphere size and spherical nature of microspheres might be due to more viscous nature of polymers solution. Also, the difference in the shape of microspheres was observed, as the microspheres containing higher number of polymers were more spherical and regular as compared to that of microspheres having lower number of polymers. The prepared mucoadhesive microspheres were found to be spherical in shape with smooth perforated surface (batch M-4) as indicated by photomicrographs. Hollow cavities could also be observed on some micrographs (batch M-2).

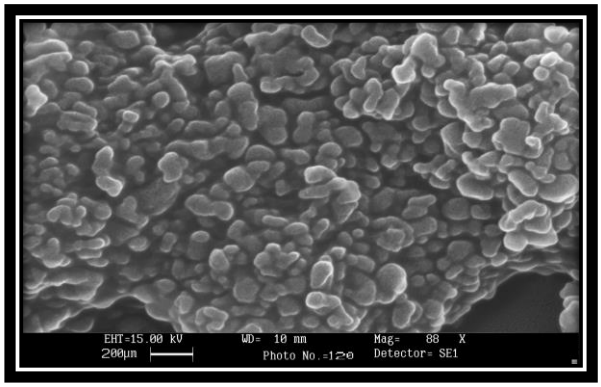

Figure 3: Scanning electron microphotograph of mucoadhesive microsphere Batch M-5.

The mean particle size of the mucoadhesive microspheres was found to be ranging from 58.32±0.14 µm to 95.72±0.66 µm. It was observed that, on increasing the polymer amount, the average particle size increased (batch M-5). The true density of the microspheres was found to be 0.151±0.065 to 0.199±0.066 g/cm$^{3.}$ The measured tapped density of the mucoadhesive microspheres was found to be in the range of 0.206±0.043 to 0.241±0.032 g/cm^3. Compressibility index ranged from 10.11±0.54 to 22.51±0.75. The angle of repose was found to be in the range of 24.11±0.66 to 35.75±0.22 (□□. All the batches showed good flow properties except bathes M-1 which exhibited higher angle of repose. Formulation M-9 showed excellent flow properties (angle of repose 24.11±0.66˚). The higher amount of glutaraldehyde appears to favor the cross-linking reaction, and hence spherical free-flowing microspheres were obtained. The

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% yield was found to be in the range of 71.33±0.25 to 92.23±0.75. It was observed that with increase polymer concentration, the % yield also increases (batch M-5). The drug entrapment/incorporation efficiency of microspheres was found to be satisfactory (59.21±0.28 to 74.02±0.34 %). The stirring speed had a negative effect on drug entrapment efficiency (i.e., the stirring speed increased, the particle size decreased, and thus drug entrapment efficiency decreased). As the ratio of drug-to-polymer increased, encapsulation efficiency increased (Batch M-5, 74.02±0.34); this is due to the fact that higher ratio of drug-to-polymer would produce large size droplets with decreased surface area, such that diffusion of drug from such microsphere was slow, resulting in higher encapsulation efficiency.

Table 2: Physical properties of mucoadhesive microsphere of batches

Batch Code	Mean Particle Size [a] (µm)	True Density[b] (g/cm^3)	Tapped Density[b] (gm/cm^3)	Compressibility Index[b] (%)	Angle of Repose[b] (q)
M-1	58.32±0.14	0.179±0.035	0.231±0.054	22.51±0.75	35.75±0.22
M-2	64.13±0.56	0.173±0.012	0.212±0.066	18.39±022	28.76±0.53
M-3	71.65±0.43	0.167±0.074	0.206±0.043	18.93±061	30.01±0.54
M-4	84.54±0.21	0.156±0.022	0.179±0.032	12.84±011	27.33±0.76
M-5	95.72±0.66	0.151±0.065	0.168±0.075	10.11±0.54	25.02±0.15

Table 3: Physical properties of mucoadhesive microsphere of batches

Batch code	Yield[a] (%)	Incorporation efficiency[a] (%)	Swelling index	Mucoadhesion [a] (%)
M-1	71.33±0.25	61.22±0.15	1.15 ± 0.45	61.12± 0.45
M-2	76.95±0.54	63.01±0.12	1.36 ± 0.75	66.21±0.76
M-3	82.43±0.61	67.45±0.96	1.48 ± 0.33	71.65±0.32
M-4	88.54±1.02	71.33±0.65	1.62 ± 0.44	74.32±0.65
M-5	92.23±0.75	74.02±0.34	1.93 ± 0.94	78.02±0.55

The swelling index of mucoadhesive microspheres was found to be in the range of 1.08±0.62 to 1.93±0.94. Swelling studies showed that the amount of polymer plays an important role in solvent transfer. It can be concluded that an increasing in polymer concentration, the swelling index also increased (batch M-5). The percentage mucoadhesion of microspheres was found to be ranges from 58.11±0.43 to 78.02±0.55. On increases the concentration of polymer the particle size increases. It was observed that the polymer to drug ratio increases, the percentage of mucoadhesion also increases (batch M-5, 78.02±0.55). The release of drug from mucoadhesive microspheres was assessed in 0.1N HCl (pH 1.2) up to 12 hours. The cumulative percent drug released after 12 hrs was found to be between 79 – 94 %. Chitosan mucoadhesive microspheres are known to swell in aqueous environments, due to hydration. As a new polymeric structure is formed by introducing bridges between polymeric chains during the cross-linking procedure, such a structure can be characterized by lower and slower penetration of the solvent through the chain structure of the polymer, suggesting that the

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swelling ratio and hence the drug release characteristics of the microsphere can be controlled by varying the content of the cross-linking agent used during the manufacturing process. The drug release from mucoadhesive microsphere batches M-1, M-2 and M-5 followed Peppas Korsmeyer model, The release of drug from all batches was found to be Fickian type except the batches M-4, M-5 because the value of 'n' for this all batch was noted to be more than 0.5. The optimized formulation M-5 which is more suitable for sustained release upto 18 h, follows zero order kinetics (R^2 0.981), best fitted with Korsmeyere Peppas (r^2 0.986) model and non-fickian diffusion (n value 0.595) dominates the drug release through the swellable matrix and hydrophilic pores.

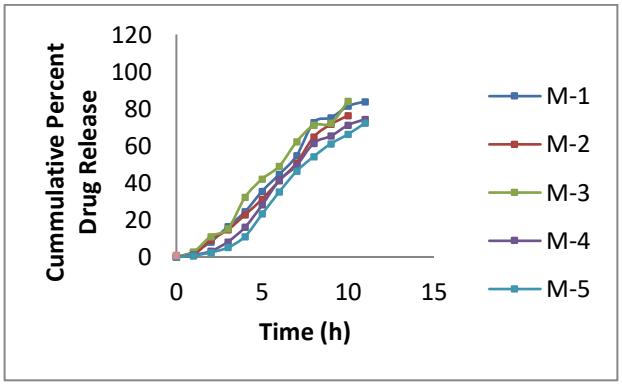

Figure 3: *in-vitro* drug release study (Zero-order kinetics) of mucoadhesive microsphere of batches (M-1 to M-5)

Summary And Conclusion: In the present work three types of dosage forms were developed mucoadhesive microspheres using biodegradable polymers like Chitosan, Carbapol. These polymers are selected on the basis that they are approved by FDA and widely used in pharmaceutical industry. The synergic drug delivery system combining a buoyant structure with bioadhesive properties could prolong the retention in the stomach. Therefore, ucoadhesive formulation based on floating microsphere is a feasible approach for sustained release drug preparations, suitable for use as gastric-retentive delivery systems. Chitosan containing mucoadhesive microspheres are known to swell in aqueous environments, due to hydration. As a new polymeric structure is formed by introducing bridges between polymeric chains during the cross-linking procedure, such a structure can be characterized by lower and slower penetration of the solvent through the chain structure of the polymer, suggesting that the swelling ratio and hence the drug release characteristics of the microsphere can be controlled by varying the content of the cross-linking agent used during the manufacturing process. Chitosan mucoadhesive microspheres are known to swell in aqueous environments, due to hydration. As a new polymeric structure is formed by introducing bridges between polymeric chains during the cross-linking procedure, such a structure can be characterized by lower and slower penetration of the solvent through the chain structure of the polymer, suggesting that the swelling ratio and hence the drug release characteristics of the microsphere can be controlled by varying the content of the cross-linking agent used during the manufacturing process.

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