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PREPARATION AND EVALUATION OF MUCOADHESIVE MICROSPHERES OF DILTIAZEM HYDROCHLORIDE

Prashantha A *, Y. Anand Kumar and Murthy PNVN

Department of Pharmaceutics, V.L. College of pharmacy, Raichur, Karnataka, India.
* Corresponding Author

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ABSTRACT

The objective of this study was to formulate and evaluate diltiazem hydrochloride (DH) mucoadhesive microspheres (MS) using sodium alginate with pectin, carbopol and HPMC. DH has a half-life of about 6 hrs and is taken twice daily in large number of patients which leads to patient compliance. DH-MS were prepared by orifice ionic gelation method using sodium alginate as coating polymer and pectin, carbopol and HPMC as mucoadhesive polymers. The prepared MS were evaluated for particle size, FTIR study, swelling ratio, *in vitro* wash off test and *in vitro* drug release. DH-MS were found to be spherical, discrete, free flowing, % mucoadhesive property and swelling index was good in all the formulations. The drug release was better at 1:3 core: coat ratio than the 1:1 and 1:2 ratios irrespective of mucoadhesive polymers. *In vitro* drug release suggests the best fit model was found to be Korsemeyer peppas and with 'n' value was less than 0.5 indicating drug release mechanism is Fickian diffusion and diffusion controlled. All the formulations showed optimum drug release at the end of desired period. F-3, F-6, F-9 was found to be optimum which showed maximum drug release over an extended period of 24 h with maximum microencapsulation efficiency and good mucoadhesive property.

Keywords: Diltiazem hydrochloride; Pectin; Sodium alginate; Carbopol; HPMC; Orifice ionic gelation.

1 INTRODUCTION

Orally controlled release systems remain the most prominent among all drug delivery systems. This has many advantages compared to conventional systems, such as better plasma level profile, lower dosing, and toxicity, etc[1]. Drug delivery systems (DDS) that can precisely control release rates or target drugs to particular body locations have had a profound effect on the healthcare system. Throughout treatment, the optimal drug delivery system delivers drugs at a pace determined by the body's needs and delivers the active entity specifically to the site of action. Through the coupling of drugs to carriers such as Microspheres, Nanoparticles and Liposome, amongst others, the carrier technology ensures an intelligent approach in drug delivery to modulate the release and the absorption of the drug[2]. Many approaches are taken with a sustainable controlled release to deliver a drug to the target site[3]. The most convenient and preferred mode of distribution to the body's systemic circulation is the oral administration of medicinal products. However, due to their inability to restrain and localize the system at the gastrointestinal tract, oral administration of most medications in conventional dosage forms has a short-term limitation[4]. Microspheres are a type of novel drug delivery system comprised of different polymers and also have a variety of applications[5]. For many years, microsphere carrier systems produced from naturally occurring biodegradable polymers have sparked significance in the development of sustained

drug delivery. Recently, dosing forms which can precisely control release rates and target drugs to a specific body site have had an important impact on the formulation, production and delivery of new drug delivery systems. The development of an oral controlled release mucoadhesive multiparticulate device is one of many methods being explored to extend the gastric residence time of the dosage form at the absorption site. This can be accomplished by combining bioadhesion properties with microspheres to create "Mucoadhesive microspheres." Due to the high surface-to-volume ratio, much more intimate contact with the mucus layer, and the precise targeting of drugs at the absorption site, mucoadhesive microspheres provide advantages such as efficient absorption and improved bioavailability of drugs[6]. Diltiazem hydrochloride, a calcium channel blocker, is widely used for the treatment of angina pectoris, hypertension and arrhythmias. It is administered orally (tablets, capsules, sustained release tablets/capsules) and parenterally (intravenous). The usual dose of Diltiazem is 180-240 mg/day. The conventional tablet and capsule is administered 3 or 4 times a day due to its short biological half-life of about 6 h. The problems of frequent administration and variable low bioavailability (40-60%) after oral administration of conventional tablet or capsules have been attenuated by designing diltiazem in the form of sustained release tablet or capsules. The mucoadhesive microspheres of diltiazem would prolong the residence time at the absorption site to facilitate intimate contact with the absorption surface and thereby improve and enhance the bioavailability. Researchers have formulated oral controlled release products of diltiazem by various techniques. Dosage forms that are retained in the stomach would increase the absorption, improve drug efficiency and decrease dose requirements[7]. In the present investigation an attempt was made to prepare mucoadhesive microspheres of Diltiazem hydrochloride intended for the treatment of high blood pressure and to control angina pectoris by using novel polymers.

2 MATERIALS AND METHODS

2.1 MATERIALS

The drug Diltiazem hydrochloride was obtained as a gift sample from Arrow chemicals Ltd, Mumbai. Sodium alginate, HPMC, Carbopol and Pectin were procured from Sd Fine Chemicals Ltd. Mumbai. All other reagents used were analytical grade and distilled water was used throughout the study.

2.2 METHODS

2.2.1 Preparation of mucoadhesive microspheres

DH-MS were prepared by orifice ionic gelation method[8] during preparation sodium alginate and mucoadhesive polymer HPMC/Pectin/Carbopol were dissolved in purified water (10 ml) separately. Then both the solutions were mixed to form homogeneous polymer solution. The DH was added to the polymer solution and mixed thoroughly with the help of pestle and mortar to form viscous dispersion. The resulting dispersion was added drop wise into 10% w/v calcium chloride solution (100 ml) through a syringe with needle (size no 21) with continuous stirring at 50 rpm. The added droplets were retained in the calcium chloride solution for 15 min to produce spherical rigid microspheres. The microspheres were collected by decantation and the product thus separated was washed repeatedly with water and dried at 45^0C for 12 h and stored in desiccators. Similarly other mucoadhesive microspheres prepared by dissolving required quantity of sodium alginate and mucoadhesive polymers (HPMC, carbopol, pectin) in water. Then drug was added to polymeric solution and mixed thoroughly with help of pestle and mortar to form viscous dispersion.

2.3 Evaluation of mucoadhesive microspheres[9-11]

2.3.1 Production yield

The dried microspheres of each batch were weighed separately and percentage yield was calculated by using following equation.

2.3.2 FTIR studies

The compatibility between DH and better DH-MS were detected by IR spectra obtained on Perkin Elmer 1600 series, (USA). The pellets were prepared on KBr press. To prepare the pellets, a few mg of the microspheres were ground together in a mortar with about 100 times quantity of KBr. The finely ground powder was introduced into a stainless steel die. The powder was then pressed in the die between polished stainless steel anvils at a pressure of about $10t/in^2$. The spectra were recorded over the wave number range of 4000 to 500 cm^{-1}.

2.3.3 Encapsulation efficiency

100 mg of mucoadhesive microspheres were accurately weighed. They were powdered and extracted with 100 ml of 0.1N HCl. Further it was serially diluted with 0.1N HCl. The resulting solution was analysed for DH content by measuring absorbance in a UV spectrophotometer at 235.5 nm using 0.1 N HCl as blank. The studies were carried out in triplicate. Encapsulation efficiency (%) was calculated using the formula.

$$\text{Encapsulation efficiency} = \frac{\text{Actual drugcontent}}{\text{Theoretical drugcontent}} \times 100$$

2.3.4 Estimation of drug content

Microspheres equivalent to 25 mg of DH were powdered and taken into a 100 ml volumetric flask. They were lysed with 50 ml of methanol for the effective extraction of drug and it was shaken for 15 min. The clear solution was diluted to 100 ml with 0.1 N HCl and then it is filtered. Then 1 ml of this filtrate was diluted to 10 ml with buffer. The drug content was analyzed by measuring absorbance in a UV spectrophotometer at 235.5 nm using 0.1 N HCl as blank. The studies were carried out in triplicate.

$$\text{Percentage yield} = \frac{\text{Practical weight}}{\text{Theoretical weight}} \times 100$$

2.3.5 Size analysis of microspheres

Different sizes in a batch were separated by sieving using a range of standard sieves 12/16, 16/22 and the amounts retained on different sieves were weighed. Studies were carried out in triplicate. The average sizes of the microspheres were calculated by using the equation.

$$\mathbf{D_{Avg}} = \frac{\mathbf{\sum Xifi}}{\mathbf{fi}}$$

Where,

X_i- is the mean size of the range

F_i- is the percent material retained on the smaller sieve in the size range.

2.3.6 Swelling studies by weight method

A known weight (50 mg) of microspheres were placed in basket assembly of dissolution apparatus rotated at 500 rpm in 500 ml of 0.1 N HCl solution maintained at 37 ± 0.5^{0}C and allowed to swell for the required period of time. The microspheres were periodically removed, blotted with filter paper and their changes in weights were measured during the swelling until equilibrium was attained. Finally, the weight of the swollen microspheres was recorded after a period of 6 hours, and the swelling ratio (SR) was then calculated from the formula.

$$\text{swelling index} = \frac{(\text{mass of swollen microspheres} - \text{mass of dried microspheres})}{\text{mass of dried microspheres}} \times 100$$

2.3.7 *In vitro* wash off test

The mucoadhesive property of microspheres was evaluated by an *in vitro* adhesion testing method known as wash off method. Freshly excised piece of intestinal mucosa (2 x 2 cm) from sheep were mounted onto glass slides (3 x 1 inch) with cyanoacrylate glue. Two glass slides were connected with a suitable support, about 50 microspheres were spread on to each wet rinsed tissue specimen and immediately thereafter the support was hung onto the arm of a USP tablet disintegrating test machine. When the disintegrating test machine was operated, the tissue specimen was given slowly, regular up and down moment in the test fluid (500 ml 0.1 N HCl) maintained at 37ºC. At the end of 30 min, 1h and hourly intervals up to 6 h, the number of microspheres adhering to tissue were counted.

2.3.8 *In vitro* drug release studies

The release of DH from mucoadhesive microsphere was investigated in 0.1 N HCl solution as a dissolution medium (900 ml) using USP type I apparatus up to 6 hrs. After 6 hrs phosphate buffer pH 6.8 was used as dissolution medium up to 12 hrs, later phosphate buffer pH 7.2 was used till end of the dissolution studies. A sample of microspheres equivalent to 50 mg of DH was taken in the basket. A speed of 50 rpm and temperature of 37 ± 0.5^{0}C was maintained throughout the experiment. At fixed intervals, aliquots (5 ml) was withdrawn and replaced with fresh dissolution media. The concentration of drug released at different time intervals was then determined by measuring the absorbance using spectrophotometer at 235.5 nm against blank. The studies were carried out in triplicate. The *in vitro* dissolution data of mucoadhesive microspheres were tabulated and calculated by using dissolution software viz., PCP DISSO V3.

3 RESULTS

3.1 Drug content studies

The amount of drug recovered from the formulated batches were studied and percentage drug content was calculated for all the batches and was presented in table 1.

Table 1: Drug content of mucoadhesive microspheres.

Batches	Theoretical drug content (mg)	Practical drug content* ± SD (mg)	Percentage drug content* ± SD
F-1	25	22.93 ± 0.277	91.72± 0.694
F-2	25	23.12 ± 0.005	92.48± 0.170
F-3	25	23.31 ± 0.268	93.24 ±0.306
F-4	25	23.00 ± 0.126	92.00 ± 0.144
F-5	25	23.18 ± 0.398	92.72 ± 0.187
F-6	25	23.37 ± 0.010	93.50 ± 0.683
F-7	25	23.81 ± 0.215	95.24 ± 0.589
F-8	25	23.87 ± 0.314	95.48 ± 0.472
F-9	25	23.81 ± 0.248	95.24 ± 0.725

*Average of three determinations

3.2 FTIR studies

The FTIR spectra of Diltiazem hydrochloride, sodium alginate, HPMC, carbopol, pectin and in combinations were presented in figures 1-3.

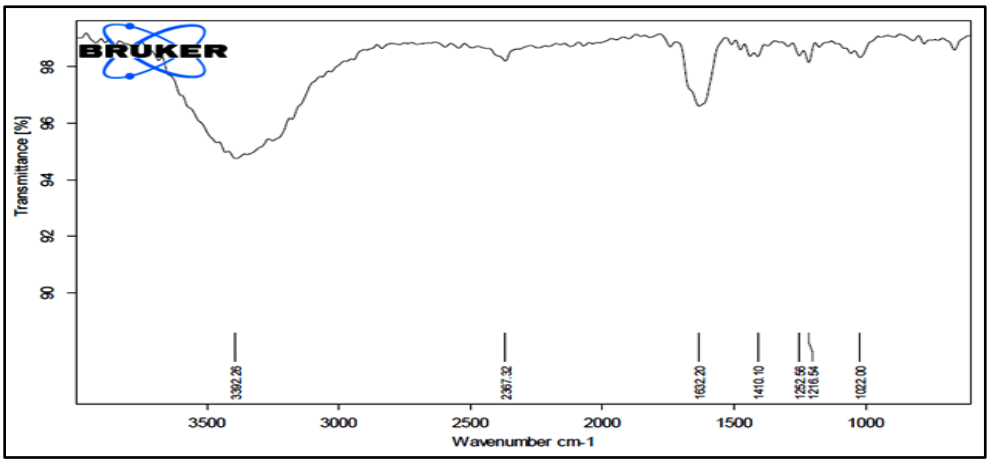

Figure 1: FTIR spectra of F3 formulation

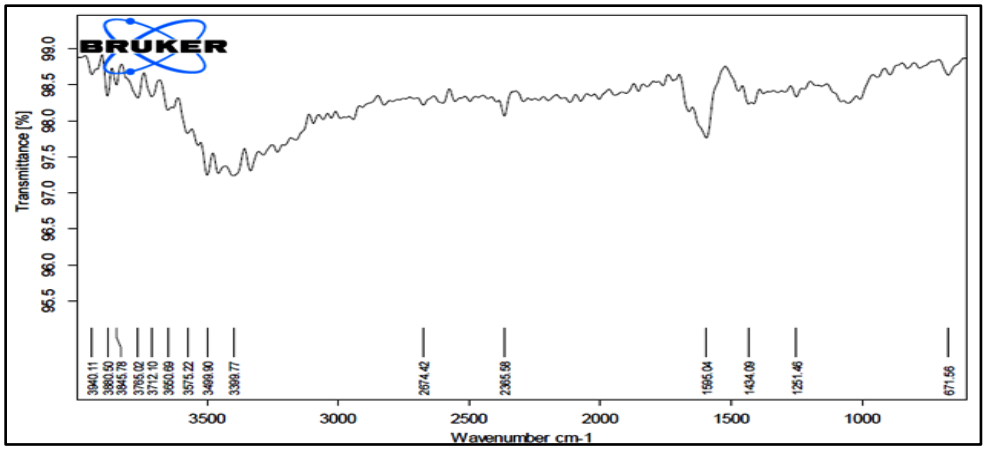

Figure 2: FTIR spectra of F6 formulation.

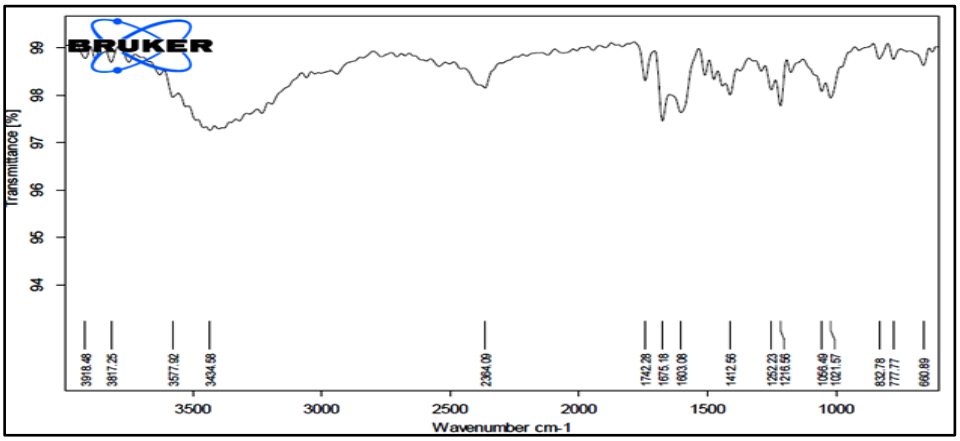

Figure 3: FTIR spectra of F9 formulation.

3.3 *In vitro* wash off test

In vitro wash off test was carried out for all the prepared batches and the results were presented in tables 2-4.

Table 2: *In vitro* wash off test data of F-1, F-2 and F-3 mucoadhesive microspheres

Batches	No. of microspheres taken	Percentage of microspheres adhering to tissues at different time intervals in hrs						
		0.5	1.0	2.0	3.0	4.0	5.0	6.0
F-1	50	90	86	78	72	69	66	64
F-2	50	92	90	80	74	71	68	67
F-3	50	98	90	84	78	70	66	60

Table 3: *In vitro* wash off test data of F-4, F-5 and F-6 mucoadhesive microspheres.

Batches	No. of microspheres taken	Percentage of microspheres adhering to tissues at different time intervals in h						
		0.5	1.0	2.0	3.0	4.0	5.0	6.0
F-4	50	92	91	87	85	83	82	80
F-5	50	94	93	90	87	85	83	82
F-6	50	94	88	80	70	64	61	60

Table 4: *In vitro* wash off test data of F-7, F-8 and F-9 mucoadhesive microspheres.

Batches	No. of microspheres taken	Percentage of microspheres adhering to tissues at different time intervals in h						
		0.5	1.0	2.0	3.0	4.0	5.0	6.0
F-7	50	94	91	87	80	72	70	67
F-8	50	95	92	90	84	74	71	69
F-9	50	92	88	84	80	72	66	62

3.4 Dissolution studies

In vitro dissolution of all the prepared mucoadhesive microspheres were studied by using USP apparatus- I basket method. The dissolution data, dissolution profiles with model fitting curves and data were presented in figure 4-6.

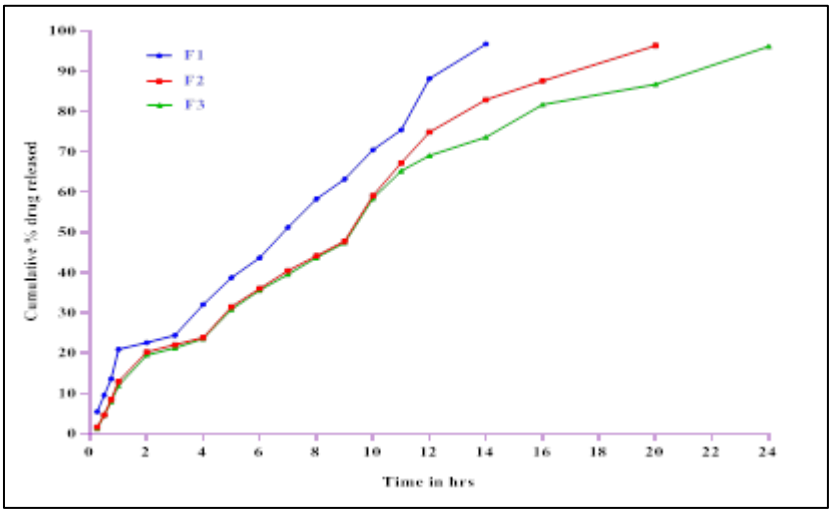

Figure 4: Comparative dissolution profile of F-1, F-2 and F-3 formulations.

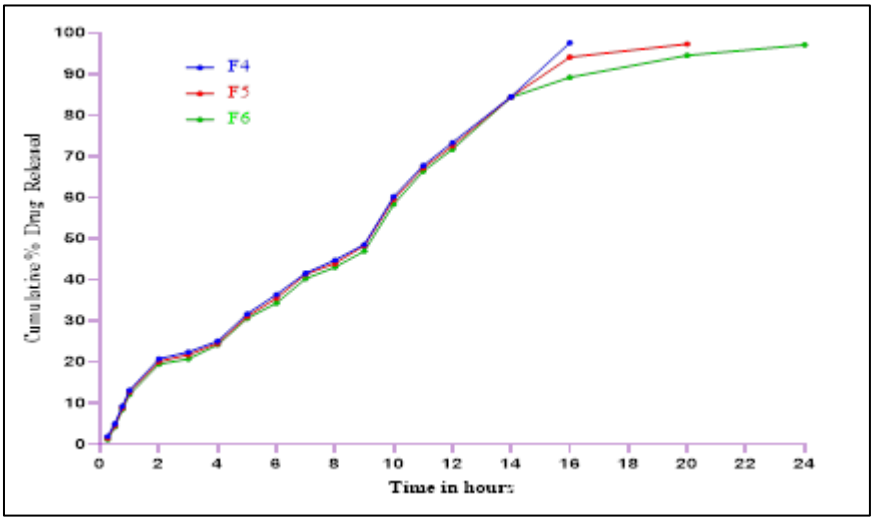

Figure 5: Comparative dissolution profile of F-4, F-5, and F-6 formulations.

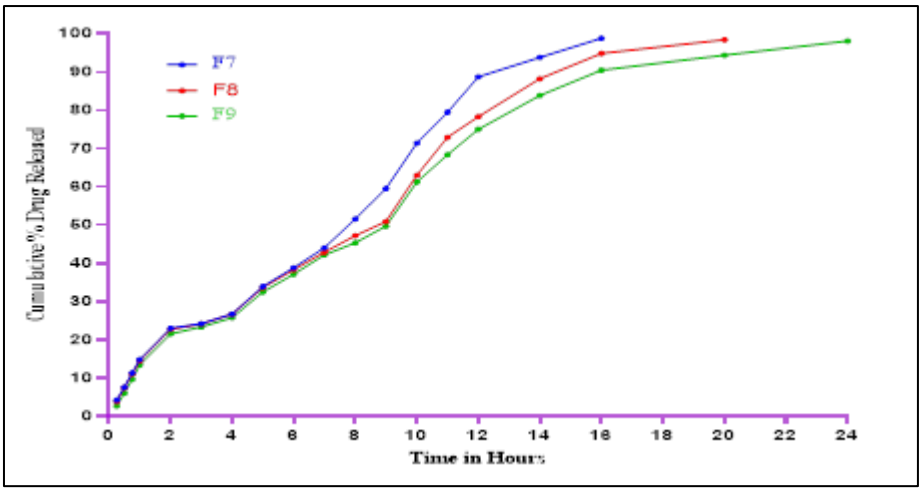

Figure 6: Comparative dissolution profile of F-7, F-8, and F-9 formulations.

4 DISCUSSION

The mucoadhesive microspheres of DH were prepared by orifice-ionic gelation method using different ratios of sodium alginate: mucoadhesive polymers. The sodium alginate was selected to control the release rate and HPMC, carbopol and pectin were selected as mucoadhesive polymers. The mucoadhesive microspheres were prepared in the ratio of 1:1, 1:2 and 1:3 core: coat (coat composition was rate controlling polymer: mucoadhesive polymer at 3:1 weight ratio). In set-I three formulations viz., F-1, F-2, F-3 were formulated with carbopol, set-II three formulations viz., F-4, F-5, F-6 formulated with HPMC, set-III three formulations viz., F-7, F-8, F-9 formulated with pectin. The percentage drug content was found to be in the range of 91.72 ± 0.694 to 95.48 ± 0.472 for F-1 to F-9 formulations. The low SD value indicates uniform distribution of drug within the various batches of microspheres prepared. Drug polymer compatibility studies were carried out using Fourier Transform Infrared spectroscopy to establish any possible interaction of Diltiazem hydrochloride with the sodium alginate, HPMC, carbapol and pectin polymers used in the formulation. The FT-IR spectra of the formulations were compared with the FT-IR spectra of the pure drug. The results indicated that the principle peaks obtained from the combinations were almost similar to that of pure drug without any significant change in their position, indicating no chemical interaction between drug and polymers. The size of the mucoadhesive microspheres in set-I was found to be 1152.40 to 1173.40 µm. The size of microspheres is depending upon concentration of sodium alginate used in the formulation. The F-1 to F-9 formulations prepared with HPMC, carbopol and pectin respectively at higher concentrations of sodium alginate shows good particle size. The swelling depends upon the polymer concentration, ionic strength as well presence of water. The Percentage relative swelling was found in the range of 120 to 280 for F-1 to F-9 formulations at the end of 6 h. In all set of formulations as the concentration of sodium alginate increases the relative swelling ratio increases which further depend on the type of mucoadhesive polymers. The mucoadhesion is a phenomenon in which two materials, at least one of which is biological are held together by means of interfacial force. The *in vitro* mucoadhesion data of mucoadhesive microspheres carried out with everted sheep intestinal mucosa in presence of 0.1 N HCl. The percentage of microspheres retained on everted intestinal mucosa after 6 h was found in the range of 62 82 for F-1 to F-9 formulations. In all set of formulations as the concentration of sodium alginate increases the mucoadhesive property increases which further depend on the type of mucoadhesive polymers. The results clearly shows better mucoadhesive property in mucoadhesive microspheres prepared with 1:3 ratio when compared to 1:1 and 1:2 ratio. The cumulative percentage drug release of mucoadhesive microspheres prepared with sodium alginate: carbopol at 1:3 ratios was found to be in 96.22 at 24th hr, with sodium alginate: HPMC at 1:3 ratios was found to be in 97.12 at 24th hr, sodium alginate: pectin at 1:3 ratios was found to be in 98.08 at 24th hr. In these results the mucoadhesive microspheres prepared at 1:3 core: coat ratio shows better drug release profile than the 1:1 and 1:2 core: coat ratios this is due to higher the concentration of the polymer greater the retardation of the drug release. In all the formulations the best fit model was found to be peppas with exponent `n` value was found to be less than 0.5 for F-1 to F-9 formulations. From the kinetic studies reveals that the best fit model was found to be peppas equations with exponent `n` value was less than 0.5 indicate the release mechanism was found to be fickanian diffusion.

5 CONCLUSIONS

The mucoadhesive microspheres of Diltiazem hydrochloride were conveniently prepared by orifice-ionic gelation method using sodium alginate and mucoadhesive polymers HPMC, carbopol and pectin. The production yield was manageable with little loss of drug during the formulation. The drug content results suggest a negligible loss of drug during the formulation stage. The increase in size of microspheres was observed with increase in concentration of sodium alginate. This could be due to increase in viscosity of the polymeric dispersion, which eventually lead to

formation of bigger particle during ionic gelation. The results clearly shows higher relative swelling ratio in mucoadhesive microspheres prepared with 1: 3 ratio than 1:1 and 1:2 ratios. In case of *in vitro* dissolution studies results showed that the mucoadhesive microspheres prepared at 1:3 core: coat ratio shows better drug release profile than the 1:1 and 1:2 core: coat ratios this is due to higher the concentration of the polymer greater the retardation of the drug release. The dissolution profiles suggest there was no significant difference in the release rate of all these formulations.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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Disclosure of conflict of interest

There is no conflict of interest.

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