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FORMULATION AND EVALUATION OF VILDAGLIPTIN MICROPHERES

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ABSTRACT

Microspheres were found to be more efficient for controlled drug delivery systems, further the mucoadhesion provides feature of targeted drug delivery to the dosage form. Mucoadhesion ensures increased contact time of the dosage form with the absorption site while microspheres sustained the release of drug from the dosage form at the site of absorption and result into improved bioavailability of drug. The objective of the present research is to formulate mucoadhesive microspheres of vildagliptin, to achieve reduced dosing frequency, increased bioavailability, increased patient compliance and decreased drug related adverse effects. This objective is achieved by formulating the mucoadhesive microspheres of the drug using orifice ionotropic gelation technique. Sodium alginate is used as a polymer while calcium chloride as counterion and HPMC K4M as mucoadhesive polymer. The formulation batches were prepared by 3^2 factorial design and evaluated for particle size, flow properties, mucoadhesion, microencapsulation efficiency, drug release and stability. The formulation SF6 showed nearly spherical microcapsules, good flowability, microencapsulation efficiency, mucoadhesion, stability and extended drug release upto 12 hours. An approach to develop a stable mucoadhesive microspheres of oral hypoglycemic drug, Vildagliptin has been successfully achieved.

KEYWORD:- Orifice ionotropic gellation, Sodium alginate, $CaCl_2$, HPMC K4M.

INTRODUCTION

Microencapsulation is a process by which the droplets or particles of liquid or solid material are surrounded or coated with a continuous film of polymeric material, resulting into the capsules ranging from less than one micron to several hundred microns in size. Microcapsules may be spherical in shape, with a continuous wall surrounding the core, while others are asymmetrically and variably shaped. These microspheres or microparticles or microcapsules can be prepared by using natural or synthetic polymers.[1] The most acceptable and convenient method of drug administration is the oral route because of its ease of administration. One limitation related with the oral delivery is poor bioavailability and for the drug candidates who show absorption window in the proximal gut and is the major obstacle to the development of controlled release formulation.[2] Mucoadhesive microspheres is one of such advances in drug delivery system which ensure the drug targeting and retention at the site of absorption to facilitate contact between the dosage form and absorption surface to improve the bioavailability of drug. The main objective of this delivery system is to control the release profile of drug and also to sustain the drug release. Bioadhesive microspheres have major advantages like efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer and specific targeting of drugs to the absorption site.[3] Microencapsulation has been accepted as a process to achieve controlled release. The selection of the technique for the preparation of microcapsules depends on many factors such as the drug solubility and short half-life of drug. Present study is related with the development of mucoadhesive microspheres of vildagliptin which resulted into sustained and localized release of the drug in the stomach.

Diabetes (Diabetes mellitus), a metabolic disorder has a condition in which the amount of glucose in the blood is too elevated and it's characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, and it may present with characteristic symptoms such as thirst, polyuria, blurring of vision, weight loss, risk of cardiovascular, peripheral vascular and cerebrovascular disease etc., which is controlled by using anti-diabetic drugs.[4] Vildagliptin is an antidiabetic agent which acts by inhibiting dipeptidyl peptidase-4 (DPP-4) for treating type 2 diabetes. DPP-4 inhibitors represent a new therapeutic approach to the treatment of type 2 diabetes mellitus. They inhibit the inactivation of incretins, resulting in the stimulation of glucose-dependent insulin release.4 DPP-4 inhibitors are a class

of compounds that work by affecting the action of natural hormones in the body called incretins. Incretins decrease blood sugar by increasing consumption of sugar by the body, mainly through increasing insulin production in the pancreas, and by reducing production of sugar by the liver.[5,6] Sodium alginate, a natural polysaccharide which is a mixture of polyuronic acids composed of residues of d-mannuronic acid and l-guluronic acid.[7] Alginates have the ability to form gels by reaction with divalent cations (Ca^{2+}). The gelation and crosslinking of the polymers are mainly achieved by exchange of sodium ions from the guluronic acids with divalent cations, and the stacking of these guluronic groups to form the characteristic egg-box structure. The divalent cations bind to the α-L-guluronic acid blocks in the highly cooperative manner and the size of the cooperative unit is more than 20 monomers. Each alginate chain dimerizes to form junctions with many other chains and as the result gel network are formed.[8]

MATERIALS AND METHODS

Materials

The Vildagliptin was obtained as gift sample from Aurobindo pharma Ltd. Hyderabad. Sodium alginate was obtained as gift samples from Wockhardt Ltd. Aurangabad. All the other chemicals used were of analytical grade.

Methods preformulation study

a) Characterization of drug

Vildagliptin was characterized by determining its solubility, melting point, UV curve, IR spectrum and DSC graph.

b) UV method validation of selected drug

The UV method development was done by determining λ_{max}, precision, recovery, LOD, LOQ, linearity and by preparing calibration curve.[9-12]

c) Preliminary compatibility study: The compatibility between the selected drug and polymers was studied by Differential scanning calorimetry and Infra-red spectroscopy.

Formulation study

a) Formulation of mucoadhesive microspheres of vildagliptin

Mucoadhesive microspheres of Vildagliptin was done by orifice ionotropic gelation technique. The microspheres were formulated by using different polymer to polymer ratio and concentration of calcium chloride as counter ion.[13]

Table I: Factorial batches of vildagliptin.

Sr. No.	Batch Code	Sodium alginate : HPMC K4M	$CaCl_2$ (%)
1	SF1	1 : 0.25	5
2	SF2	1 : 0.25	7.5
3	SF3	1 : 0.25	10
4	SF4	1 : 0.5	5
5	SF5	1 : 0.5	7.5
6	SF6	1 : 0.5	10
7	SF7	1 : 0.75	5
8	SF8	1 : 0.75	7.5
9	SF9	1 : 0.75	10

Preparation of microspheres

Vildagliptin mucoadhesive microspheres were prepared by orifice ionic gelation technique, using sodium alginate as the controlled release material, calcium chloride dehydrate as the cross-linking agent and HPMC K4M as mucoadhesive polymer.

The required quantity of sodium alginate (2.5%) and HPMC K4M were dissolved in 40ml of deionized water. To this solution 0.5gm of drug was dispersed and stirred to get viscous aqueous dispersion. This dispersion was then extruded through a syringe with 18# needle into 40ml $CaCl_2$ solution of required strength with continuous stirring at 500rpm. The microspheres thus formed were allowed 1 hour for curing into the calcium chloride solution. The spheres then decanted, washed several times with petroleum ether and air dried overnight at room temperature.[14]

b) Evaluation of mucoadhesive microspheres of vildagliptin physical properties determination

The particle size of the microspheres was determined by using optical microscopy method using a pre-calibrated ocular micrometer and stage micrometer. The surface of the microspheres for morphological characterization were observed via scanning electron microscopy. The flow properties of prepared microspheres were determined by bulk density, angle of repose, Carr's index and Hausner's ratio.

Estimation of drug content

Vildagliptin content in the microcapsules was estimated by a UV spectrophotometric method based on the measurement of absorbance at 212.6 nm in 0.1N HCl.

Percentage yield

The batches were weighed after drying and the yield % was calculated using the formula given below

% Yield = $\frac{W}{Wt} \times 100$ Where,

W= Practical Weight of prepared microspheres Wt= Original weight of drug and polymers.[15]

Micro-encapsulation efficiency

The prepared microspheres equivalent to 10 mg of Vildagliptin were weighed accurately and crushed. The powdered microspheres were placed in 10 ml of 0.1N HCL and kept for 24 hours. The solution was then filtered and absorbance was measured at 212.6 nm using UV spectrophotometer and the percent drug entrapped was calculated as follows.[16]

$$\%\text{Drug entrapment} = \frac{\text{Calculated Drug Content}}{\text{Theoretical Drug Content}} \text{ X } 100$$

In-vitro Wash-off test for microspheres: The mucoadhesive properties of the microspheres were evaluated by in vitro wash-off test. A 3 X 2 cm piece of goat intestine mucosa was tied onto a glass slide using thread. Weighed microspheres were spread onto the wet rinsed tissue specimen, and the prepared slide was hung onto one of the groves of a USP tablet disintegrating test apparatus as shown in "Figure 2". The disintegrating test apparatus were operated such that the tissue specimen was given regular up and down movements in a beaker containing 0.1N HCl. At the end of 1, 4 and 8 hours the weight of microspheres still adhering onto the tissue was determined after centrifugation and drying.[17]

$$\% \text{ Mucoadhesion} = \frac{Wt\ of\ microspheres\ adhered}{Wt\ of\ microspheres\ applied}\ X\ 100$$

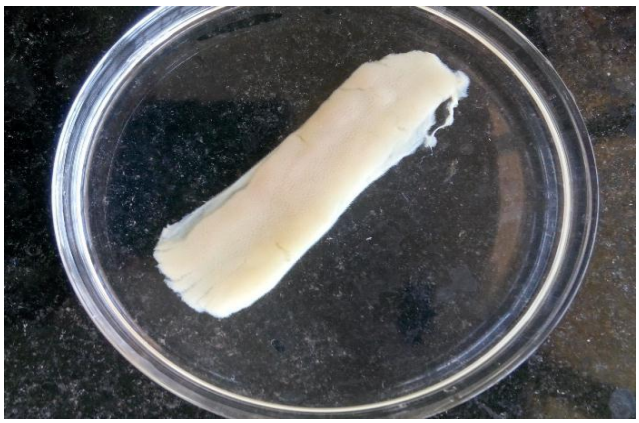

Figure 1: Goat intestine mucosa.

Figure 2: In-vitro Wash-off test.

In-vitro drug release

In vitro release studies were carried in 0.1N HCl medium. The test conditions are as follows: microspheres containing 50 mg of drug packed in a capsules were dropped into a vessels containing 900 ml of 0.1N HCl medium with the temperature maintained at 37±0.5°C. The rotating rate of the paddle of USP dissolution test apparatus was adjusted to 50 rpm. With intervals of one hour, 5 ml of samples were withdrawn and filtered through a 0.45µm membrane filter. The equivalent volume of the medium with the same temperature was added to the dissolution vessel to maintain sink condition. The absorbance values of the filtrate at the wavelength of 212.6 nm were determined and percent drug release calculated.[18,19]

Stability study

Stability studies were carried out according to International Conference on Harmonization (ICH) guidelines. The optimized batch SF6 was stored at 40 ± 2°C/ 75 ± 5% RH (relative humidity) for three months. The samples were withdrawn and evaluated for drug content, average particle size, percent muco-adhesion after 8 hours and drug release.[20,21]

RESULTS AND DISCUSSION

Mucoadhesive microspheres of vildagliptin by using sodium alginate as polymer and $CaCl_2$ as crosslinking agent were prepared by orifice ionotropic gelation technique. The optimization of the batches was done by 3^2 factorial design considering two independent factors as sodium alginate to HPMC K4M ratio and concentration of Ca Cl_2.

The purity of drug sample was confirmed by determination of its melting point, solubility, λ_{max}, DSC and IR spectrum. The melting point of the drug was found to be 107°C which is between the standard range 103 - 107°C. The λ_{max} of vildagliptin in 0.1N HCL was found to be 212.6 nm. The DSC and IR peaks were found to be similar with the standard DSC and IR peaks of the pure drug.

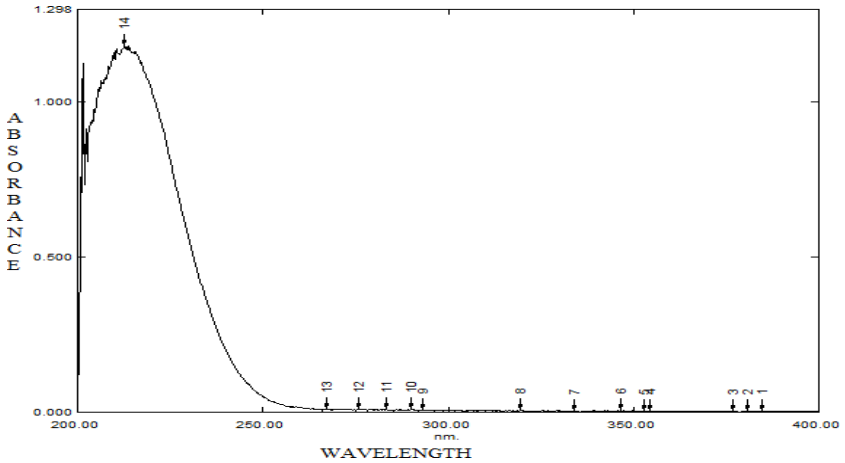

Figure 3: UV spectrum of Vildagliptin in 0.1N HCL.

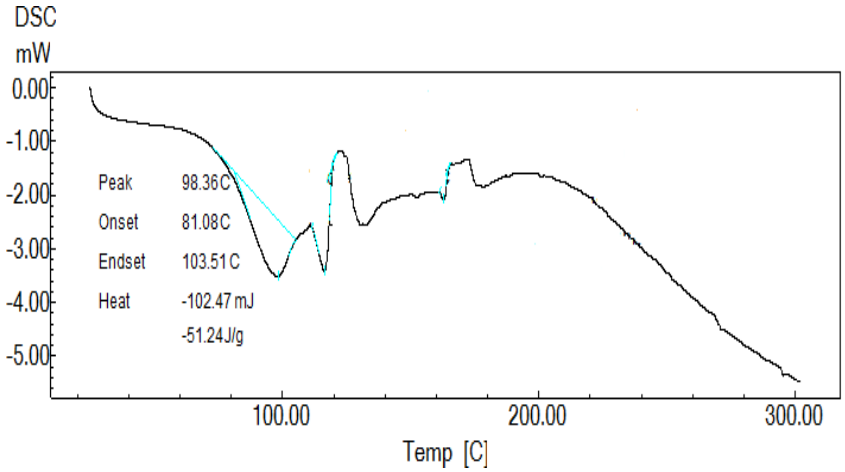

Figure 4: DSC thermogram of Vildagliptin.

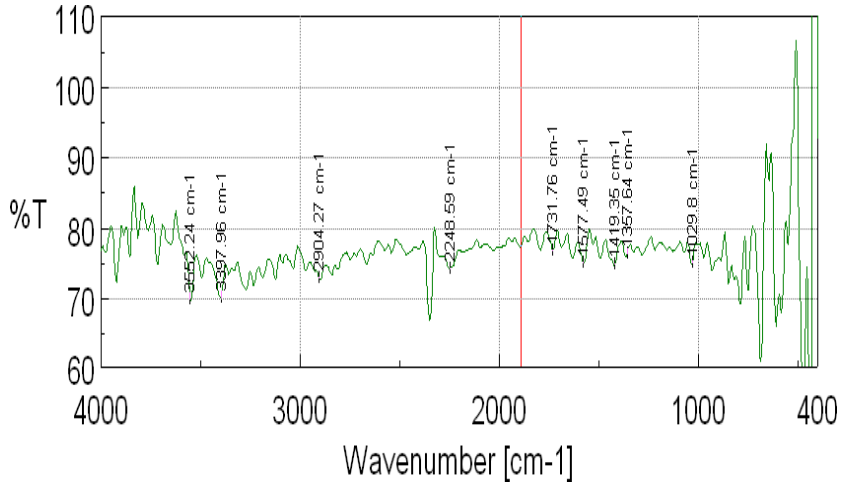

Figure 5: IR spectrum of Vildagliptin.

The UV method validation for estimation of drug vildagliptin in 0.1N HCl was done successfully with linearity, precision, recovery, LOD and LOQ. The λ_{max} was found to be 212.6 nm and the calibration curve was plotted as follow.

Table II: Calibration curve of Vildagliptin in 0.1N HCl.

Sr. No.	Concentration (mcg/ml)	Absorbance
1	5	0.13
2	10	0.26
3	20	0.52
4	30	0.74
5	40	0.97
6	50	1.19

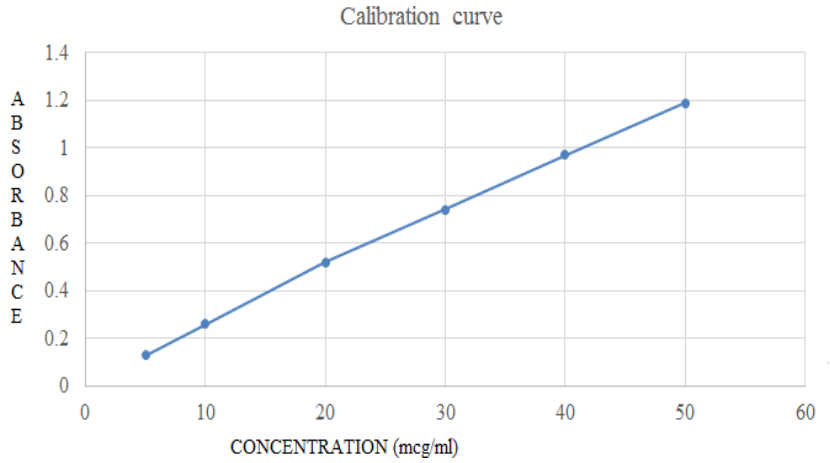

Figure 6: Standard curve of Vildagliptin in 0.1 N HCl.

The compatibility study between drug and polymers selected was done by the DSC and IR. There were no much significant changes observed between the DSC thermogram and IR spectrum of pure drug and that of the mixtures of drug and polymers.

Average particle size of microspheres of all the batches were found to be in the range of 784 to 963 µm. the surface morphology of the microspheres indicated that the spheres are nearly spherical and have rough surface "Figure 7". The flowability of particles depending upon the parameters such as angle of repose, Carr's index and Hausner's ratio was from good to excellent (table III).

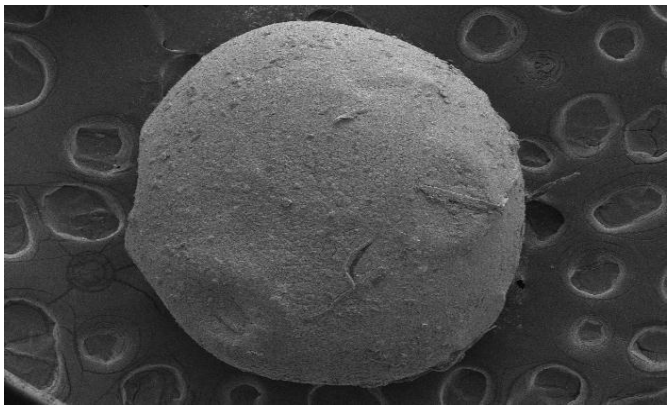

Figure. 7: SEM image of SF6 batch.

Table III: Physical properties of factorial batches.

Sr. No.	Batch code	Average particle size (µm)	Angle of repose	Carr's index	Hausner ratio	% Micro-encapsulation efficiency
1	SF1	784.06 ± 1.12	29.73 ± 0.15	13.29	1.15	84.49
2	SF2	815.4 ± 2.05	31.24 ± 0.52	12.94	1.15	89.32
3	SF3	838.17 ± 0.93	32.06 ± 0.46	13.58	1.16	93.59
4	SF4	843.8 ± 1.7	32.43 ± 0.16	13.21	1.15	89.8

5	SF5	872.72. ± 0.88	33.74 ± 0.22	14.65	1.17	95.36
6	SF6	904.52 ± 0.79	33.64 ± 0.53	14.38	1.17	94.88
7	SF7	891.42 ± 3.15	32.63 ± 0.78	14.2	1.16	90.27
8	SF8	924.06 ± 1.05	33.42 ± 0.41	14.76	1.17	96.93
9	SF9	963.19 ± 1.85	34.14 ± 0.34	15.75	1.19	97.02

Percent estimated drug content of the factorial batches varied from 20.06 to 26.74%. The percent micro-encapsulation efficiency of the batches are shown in table III. Mucoadhesion was studied by in-vitro wash-off test using goat mucosa and tablet disintegration test apparatus at 37±0.5°C upto 8 hours and the microspheres showed good mucoadhesion as shown in table IV.

Table IV: In-vitro wash-off test.

Sr. No.	Batch code	Percent Mucoadhesion		
		1 Hour	4 Hour	8 Hour
1	SF1	81.145	69.28	62.63
2	SF2	82.65	72.525	66.94
3	SF3	83.825	72.59	69.845
4	SF4	85.565	77.81	75.235
5	SF5	87.78	82.015	80.075
6	SF6	90.025	87.475	84.425
7	SF7	89.935	86.185	83.52
8	SF8	91.26	89.115	85.09
9	SF9	93.21	90.19	86.835

In-vitro drug release from the factorial batches was slow and controlled. The study revealed that with increase in particle size the release of drug decreased as particle size increases surface area decreases and diffusional path length increases which results in slow drug release, and vice-versa with decrease in particle size. With increase in stirring speed, the particle size decreased which resulted in faster drug release. With increase in the polymer and $CaCl_2$ concentration the increase in particle size of microspheres was observed. The drug release from the factorial batches are graphically represented in figure 8, 9 and 10.

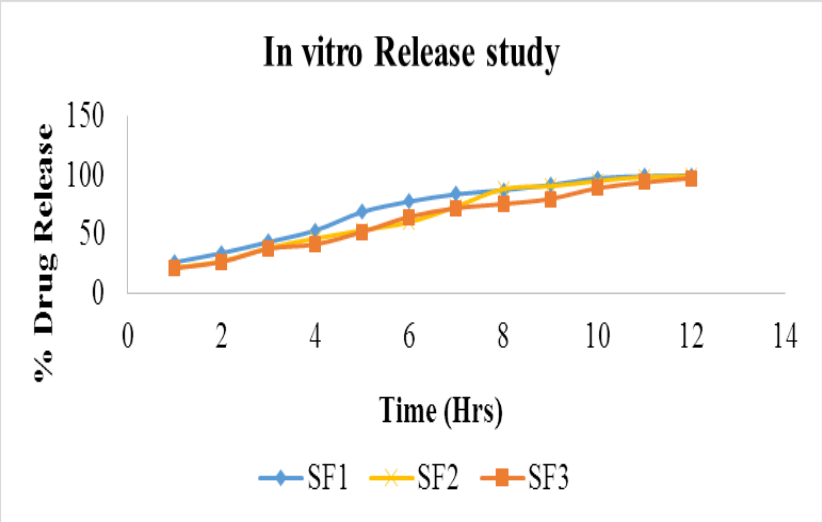

Figure 8: Percent drug release from batches SF1, SF2 and SF3.

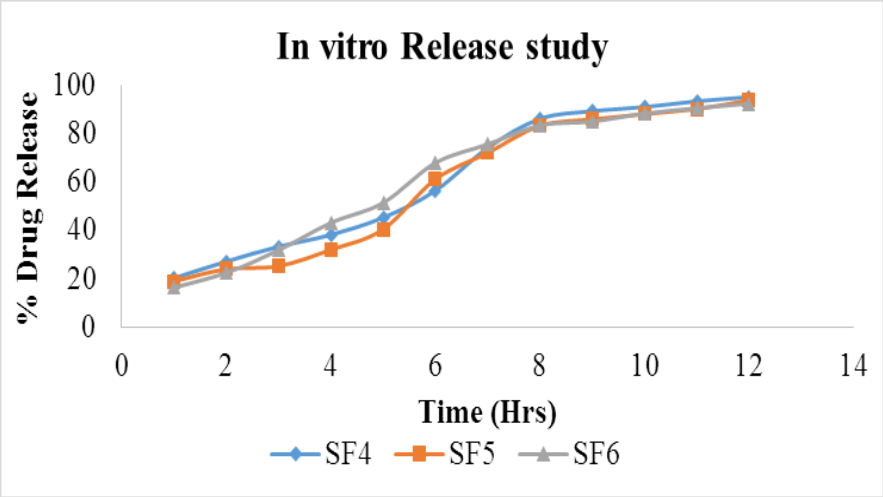

Figure 9: Percent drug release from batches SF4, SF5 and SF6.

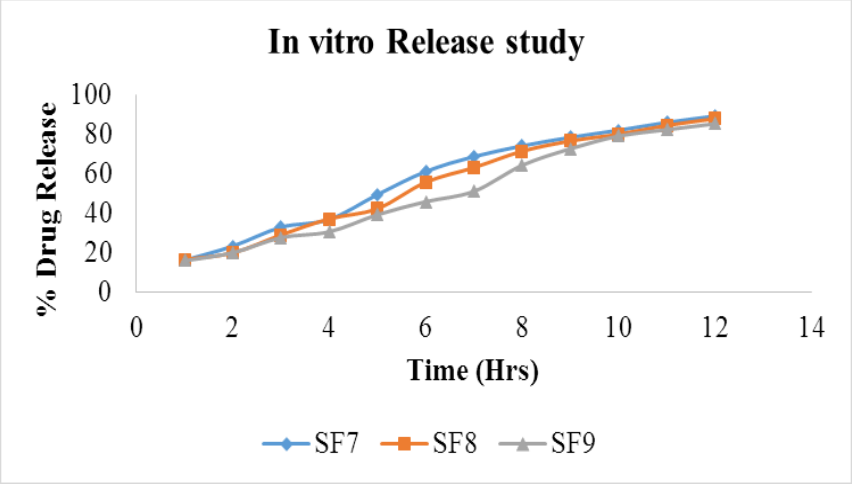

Figure 10: Percent drug release from batches SF7, SF8 and SF9.

Table V: Stability study of SF6 batch.

Sr. No.	Parameters	SF6	
		0 month	3month
1	Drug content (%)	23.72	23.56
2	Particle size	904.52 ± 0.79	918.82 ± 0.54
3	% Mucoadhesion after 8 hours	84.425	81.532
4	Drug release after 12 hours	92.29 ± 0.49	90.86 ± 0.45

The stability study of the optimized batch SF6 indicated no significant changes in drug content, average particle size, mucoadhesion and drug release.

CONCLUSION

An attempt has been made to develop a stable mucoadhesive microspheres of new drug Vildagliptin using sodium alginate and HPMC K4M by orifice ionic gelation technique. The variables sodium alginate to HPMC K4M ratio and $CaCl_2$ concentration exhibited significant effect on the release profile of drug and mucoadhesion of microspheres. With increase in concentration of polymer the increase in particle size was observed which resulted in decreased surfsce area, increased diffusional path length and thus slower drug release as well as with increase in $CaCl_2$ concentration the spheres became hard and further retard the release of drug from microspheres. The optimized batch SF6 was found to be best batch among all the factorial batches, since it showed good flow ability, mucoadhesion, fair drug entrapment and it could prolong the release of drug for longer duration. The drug release from SF6 was found to be prolonged for 12 hours. A stable mucoadhesive microspheres of oral antidiabetic drug, Vildagliptin has been successfully developed by orifice ionotropic gelation technique.

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