RESEARCH ARTICLE

Design, Fabrication and Evaluation of Vildagliptin Loaded Crosslinked Sodium Alginate and Guar Gum Microspheres

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ABSTRACT

Vildagliptin is an Anti-hyperglycemic drug. This study was based on fabrication and evaluation of Vildagliptin loaded microspheres by ionotropic gelation method. Overall six batches of microspheres with sodium alginate and guar gum microspheres had been composed and evaluated for particle size measurement with digital microscope, percentage yield, swelling index, determination of drug entrapment, scanning electron microscopic image, *In Vitro* release study of drug and release kinetics. Novelty of this study is use of different concentrations of counter ion solution and comparing improvement in drug diffusion. Evaluation studies showed that particle sizes of microspheres ranged within 0.7 to 1.1 mm, as well as scanning electron microscopy also showed good reports. Highest percentage yield was achieved for F1 that was 88.17 %. Swelling indexes were promising for all batches but the highest value noticed for F2. Drug entrapment efficiency results showed a way up value for F5. Drug release kinetic results for all six formulations indicated notable responses for Korsmeyer Peppas and Higuchi Model rather than other models. F1 gave the most mesmerizing report for Korsmeyer Peppas and Higuchi Model with diffusion controlled mechanism.

Keywords: Vildagliptin, Microspheres, Inotropic gelation method, Release kinetics.

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INTRODUCTION

Nowadays hyperglycemia or diabetes is the most commonly observed disease in patients with insufficient insulin production. Vildagliptin is Dipeptidyl Peptidase-4 Inhibitor which inhibit DPP-4 enzyme which degraded glucagon release by formulating GLP-1 or glucagon like peptide-1 and glucose dependent insulin tropic polypeptide which is able to stimulate insulin (secretion) from β cells of Pancreas. By incorporating Vildagliptin GLP-1 and GIP actions together increase with increased insulin secretion. But Vildagliptin has problems related to short half-life with low bioavailability which leads to frequent dosing and notable chances of adverse effects. To encounter these issues use of microspheres have been enlarged to reduce dosing frequency and improve drug efficacy.[1] Microspheres have ability to control extent of drug release and also release rate can be modifying by size, shape, and polymer choice of microspheres. Microspheres protect the drugfrom degradation.[2] Drug loaded microspheres can improve drug solubility, stability, improve pharmacological action and effective drug release by minimizing its side effects.However Vildagliptin microspheres prepared by Ionotropic gelation method creates hydrogel network-based microspheres with drug which is more effective and suitable.[3] The ionotropic gelation process is a straight forward and mostly applied technique for preparing microspheres, which leads to the formation of cross-linked negatively charged polymer molecules (alginate) with positively charged ions (such as aluminum or barium) to create a gel matrix.[4] In this method, in alginate solution guar gum was included for improving mechanical strength of the microspheres, stability and to control the drug release property. Gastric retention duration was increased by sodium alginate of the microspheres. Alginate containing formulations can minimize dosage frequency.[5] Prepared microspheres were evaluated for physical, chemical properties, drug entrapment, and dissolution study. Drug dissolution study differentiation will help in identifying the most suitable counter ion solution for controlling the drug release of metronidazole. Past research works were done for improvement of dosage frequency and bioavailability but omitted part was the mechanism of diffusion through pores of microspheres that can be corrected by use of different concentrations of ion solution with increased swelling property but without changing the drug and polymer ratios.

MATERIALS AND METHODS

Materials

Vildagliptin is gifted sample from reputed Pharmaceutical Company in Sikkim. Sodium alginate and guaran from guar beans were derived out of Yarrow chem. Aluminium Chloride along with Barium Chloride was belongs to Nice Chemicals Pvt. Ltd., Cochin. All listed materials are followed by analytical grade.

Methods

Preparation of Vildagliptin Microsphere by Ionotropic technique of gelation

Ionotropic technique of gelation was applied for preparing microspheres loaded with Vildagliptin by using

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Table 1: Composition of Vildagliptin loaded Microspheres

Formulation Code	Vildagliptin Drug	Sodium Alginate	Guar Gum	% of Aluminium Chloride	% of Barium Chloride
F1	100	100	100	1%	–
F2	100	100	100	–	1%
F3	100	100	100	1%	1%
F4	100	100	100	2%	–
F5	100	100	100	–	2%
F6	100	100	100	1%	2%

*Weight of ingredients are followed by 'mg'.

Table 2: Characterization of Vildagliptin Microspheres by Average particle size, Percentage yield, Swelling Index and Efficiency of Drug Entrapment

Formulation code	Average of Particle Size (mm)	Percentage of Yield (%)	Swell Index (%)	Drug Entrapment Efficiency (%)
F1	0.8	86	210	23.44
F2	1.1	85	340	34.33
F3	0.8	77	120	19.33
F4	0.9	52	70	34.89
F5	0.7	71	170	46.67
F6	0.8	88	220	19.40

biopolymers like sodium alginate and guar gum. Cross linking agents like aluminium chloride and barium chloride were included in preparation. A homogeneous solution was prepared by dissolving accurately weighed 1gm of sodium alginate in 15 ml purified water by utilising a magnetic stirrer, maintaining 200 rpm speed until it dissolved. Guar gum was also weighed and mixed with 90 ml of purified water (warm) and temperature was maintained (50°C). [6]After complete dissolution, both the polymers were mixed uniformly. In a different beaker 1 gm of Vildagliptin was mixed in purified water (15 ml) and solution of drug was poured within previous polymer mixture solution for generating solution of drug polymer. In another beaker ion solution (counter) was synthesized by addition of different concentrations of aluminium chloride else barium chloride within 100 ml water (purified) for different formulations. After complete mixing, drop-wise drug polymer solution was extruded by a flat tipped needle into the counter ion solution. The drug polymer droplets were permitted to stand for 15 minutes in a counter ion solution for the curing reaction to provide spherical shape. Then prepared microspheres were strained using a mesh strainer and cleansed for removing cross-linking agents by distilled water. Finally, microspheres were then placed in Petri dish for drying at normal room temperature.

Evaluation of Vildagliptin Microspheres

Surface morphology and Particle Size Measurement

Prepared microspheres were studied for Size distribution by optical microscope. Scanning Electron Microscopic depictions were taken by utilizing SEM model (Scanning Electron Microscope model), Hitachi 5520, at 10 kv for identifying the surface morphology and shape. The depictions were observed for confirmation of spherical morphological characteristics of the microspheres. Randomly selected optimum numbers of microspheres were measured for size measurement by using a Digital microscope. Mean diameter of microspheres was determined from all six formulations.[7]

Percentage yield

The percentage of yield is calculated by taking total weight of the initial drug and polymer which were used for microsphere generation and weight of formulated microspheres. Percentage of yield can be calculated with this formula below,[8]

$$Percentage\ of\ yield\ = \frac{Microspheres\ Weight}{Drug\ Polymer\ Weight} \times 100$$

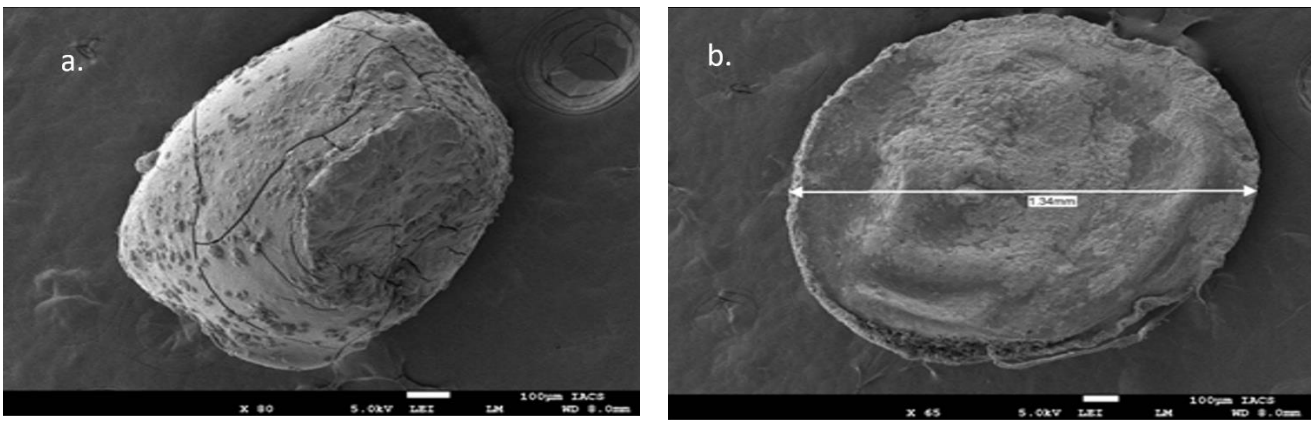

Figure 1: SEM image of Vildagliptin microspheres where a) SEM of F1 and b) SEM of F6 with diameter

Swelling Index

Dried microspheres (W_0) with measured amount 10 mg from all six formulations were taken. Swelling of microspheres were allowed for 24 hours within 1 ml media of distilled water in six separate test tubes. At 37 ◦ C and after 24 hours the weight of microspheresin swelled condition (Ws) was measured.[9] The swelling characteristics (index) wascalculated by using the formula mentioned below.

$$Swelling\ index = \frac{W_S - W_0}{W_0} \times 100$$

Drug entrapment determination

Microspheres in dried phase were measured for weight and converted into fines by applying mortar and pestle and suspended within the solution of phosphate buffer with pH 6.8. It was retained for some time which could allow maximum release of drug within medium. Finally filter the suspension and sample was measured by spectrophotometer.[10]

$$Efficiency\ of\ Drug\ Entrapment = \frac{X_1}{X_2} \times 100$$

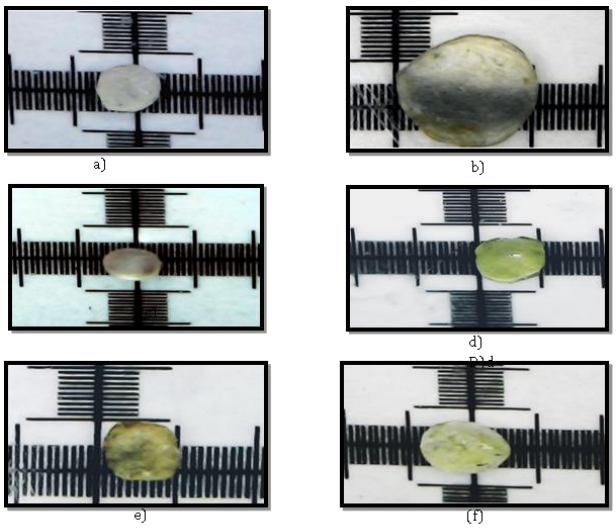

Figure 2: Microscopic figures of different formulations (Vildagliptin Microspheres) where a), b), c), d), e) and f) represents Microscopic Imaging for F1 to F6 simultaneously

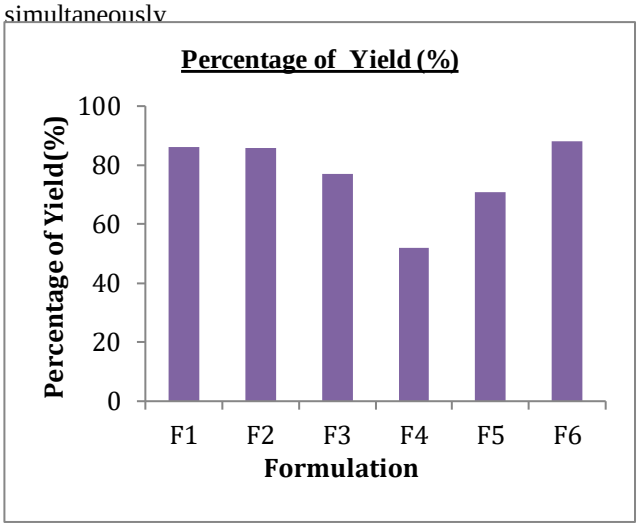

Figure 3: Percentage of yield comparison for Vildagliptin Microspheres formulations

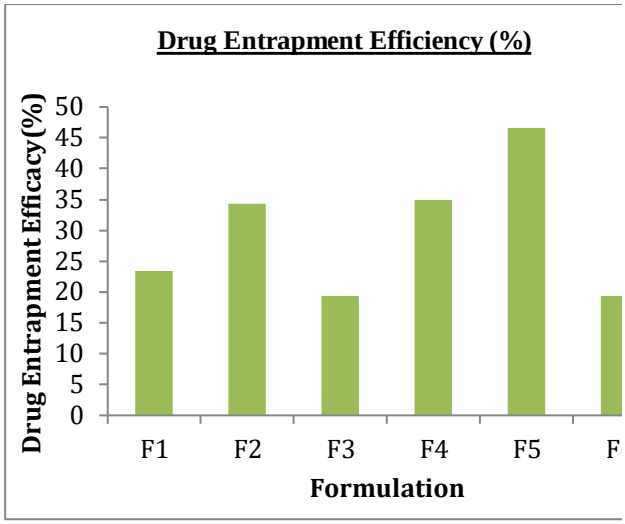

Figure 5: Drug Entrapment comparison within Vildagliptin Microspheres

Whereas, X_1 = Drug amount present in the beads experimentally and X_2 = Theoretical drug amount.

Drug release (In Vitro) study

USP (Type II) dissolution test apparatus was used for *In Vitro* release study (at 50 rpm). Measured microspheres were kept in basket by immersing it into dissolution media of phosphate buffer (900 ml), pH 6.8 at 37±0.5º C. Aliquots of 5 ml were withdrawn (15 minutes interval) up to 6 hours and diluted (5 ml buffer).[11] Sink condition was kept in dissolution apparatus. Samples were observed under UV-spectrophotometry for assay at 208 nm.[12]

Drug Release kinetics

Drug release (kinetics) study of microspheres is depending upon the size, polymer density, crosslinking agents, polarity, pH of the medium, drug release pattern through matrix and time. After collecting dissolution data, it was applied in the popular release model calculations such as Hixon–Crowell, Korsmeyer–Peppas, First-order and zero order model for checking release kinetics and predicting overall release Characteristics belongs to drug moiety through microspheres.[13, 14] Release kinetics of zero order is

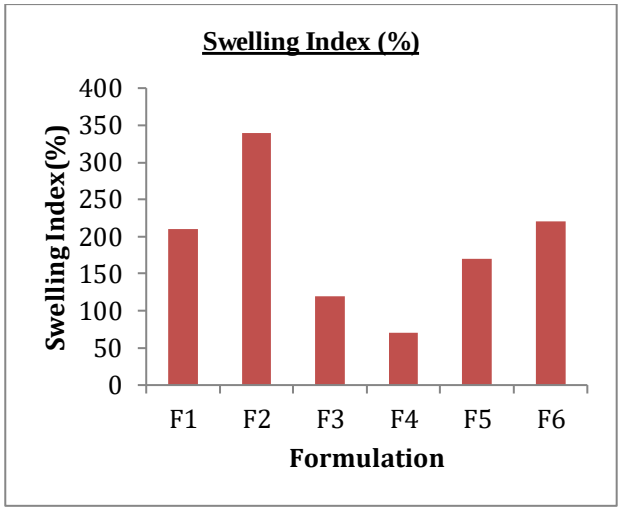

Figure 4: Swelling behaviour belongs to Vildagliptin Microspheres

Table 3: Drug Release study for Formulation 1

Time t (min)	Square root of time (minutes)$^{1/2}$	ln(t)	Amount released M (mg)	ln(M)	Amount to be released M_0-M (mg)	ln(M_0-M)	(M_0-M)$^{(1/3)}$
0	0	0	0	0	23.44	3.15	2.86
15	3.87	2.71	4.49	1.50	18.95	2.94	2.67
30	5.48	3.40	7.13	1.96	16.31	2.79	2.54
45	6.71	3.81	8.18	2.10	15.27	2.73	2.48
60	7.75	4.09	8.29	2.11	15.16	2.72	2.47
75	8.66	4.32	9.10	2.21	14.34	2.66	2.43
90	9.49	4.50	9.86	2.29	13.59	2.61	2.39
105	10.25	4.65	11.25	2.42	12.19	2.50	2.30
120	10.95	4.79	11.35	2.43	12.10	2.49	2.30
135	11.62	4.91	12.34	2.51	11.10	2.41	2.23
150	12.25	5.01	16.90	2.83	6.54	1.88	1.87
165	12.85	5.11	17.33	2.85	6.12	1.81	1.83
180	13.42	5.19	18.16	2.90	5.29	1.67	1.74
195	13.96	5.27	19.43	2.97	4.02	1.39	1.59
210	14.49	5.35	20.67	3.03	2.77	1.02	1.40

*Initial dose(M_0) = 23.44 mg

represented by Equation, $F = K_o t$; where F, t and Ko is drug fraction, release in time and zero order release constant respectively. Formula, ln (1-F) = - $K_1 t$ is for calculation of First order kinetics; where F, t and K1 represents drug fraction, release time and constant of First order release.[15] Equation, $F = K_H t_{1/2}$ is applied for Higuchi model; where F, t and K_H is drug fraction, release time and constant of Higuchi dissolution simultaneously. Formula, $Q^{1/3}$= kt $+Q_0^{1/3}$ is for Hixson-Crowell model; where drug release time t, initial value for Q is Q_0 and constant for rate is K sequentially. Equation, $F=K_p t^n$ is for Korsmeyer-Peppas model, where F, t, Kp and n represents fraction of drug, release time and Korsmeyer-Peppas rate constant, and exponent for release serially.[16]

RESULTS AND DISCUSSION

Characterization of Vildagliptin Microspheres

The characterization of various Vildagliptin microspheres (F1–F6) aimed to assess their Surface morphology, size distribution, Percentage yield, swelling index and drug entrapment efficiency which are vital determinations for formulation quality and efficacy. Electron Microscopic images by utilizing Scanning Electron Microscope model was identified the surface morphology and shape of microspheres. F1 and F6 formulation had spherical shape as expected Figure 1. Size measurement of F6 formulation by SEM shows 1.34 mm of size range which was almost near the ideal microsphere size. Size distribution of Microspheres by digital microscope shows most promising results for all formulations and ranges within 0.7 mm to 1.1 mm Figure 2. Study represents lowest size for F5 and F2 simultaneously. Previous investigations showed that the

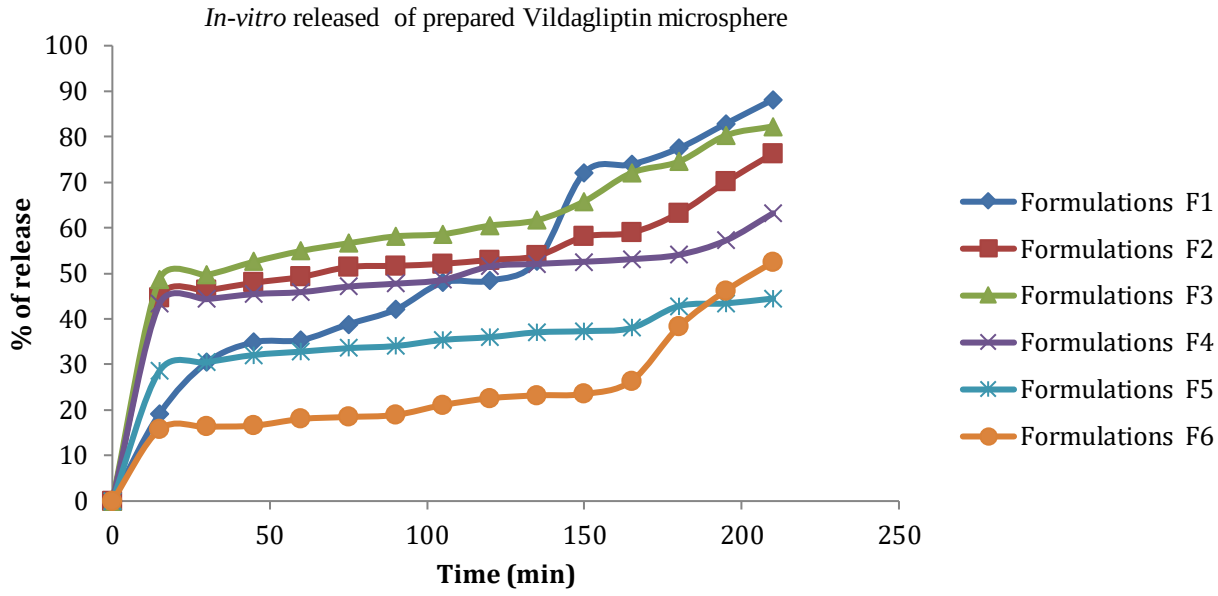

Figure 6: Drug Release (*In-Vitro)* of all Six Formulations Vildagliptin Microspheres

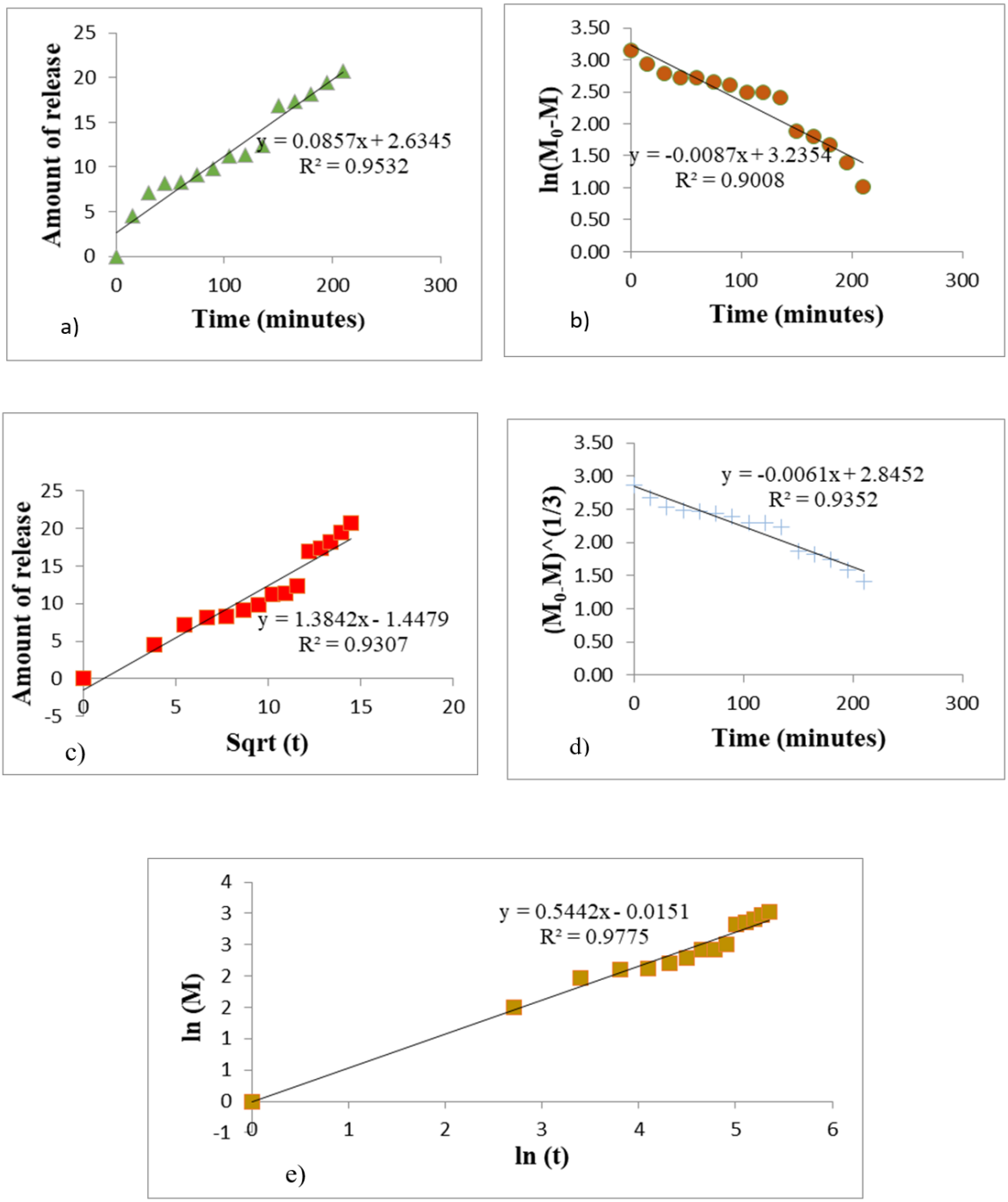

Figure 7: Kinetic Models of Formulation F1 [a) Zero Order reaction, b) First Order reaction, c) Higuchi Model, d) Hixson-crowell model and e) Korsmeyer-Peppas model]

ideal ranges of microspheres lie between 1 and 1000 µm.[17]This current study also represents all most same size distribution range. Percentage yield study results showed that F6 formulation had highest percentage yield of 88% while F4 formulation had the lowest percentage yield of about 52% Figure 3. All of the formulations except F4 formulation had promising swelling indexes. But overall study showed that F2 formulation had highest swelling index about 340 % Figure 4. Few previous studies showed that better swelling property can achieved with more than 130 % Swelling Index.[18]Drug entrapment efficiency highest value was observed for F5 while the lowest value was detected for F3 Figure 5.

Drug release study (*In Vitro*) of Vildagliptin microspheres

Formulation 1 had demonstrated controlled release profile over the 3.5 hours testing period where percent drug release increasing with time Table 3. The release profile provided evidence which indicating highest rate of drug release for F1-F3 and prolong release for several formulations like F4-F6 showed in Figure 6. Vildagliptin slowly releases drug out of matrix and into the surrounding dissolution medium,

Table 4: Regression coefficient values for Formulation F1

Formulation code	Zero Order	First Order	Higuchi	Hixson-Crowell	Korsmeyer-Peppas
F1	0.9530	0.9000	0.9300	0.9350	0.9770

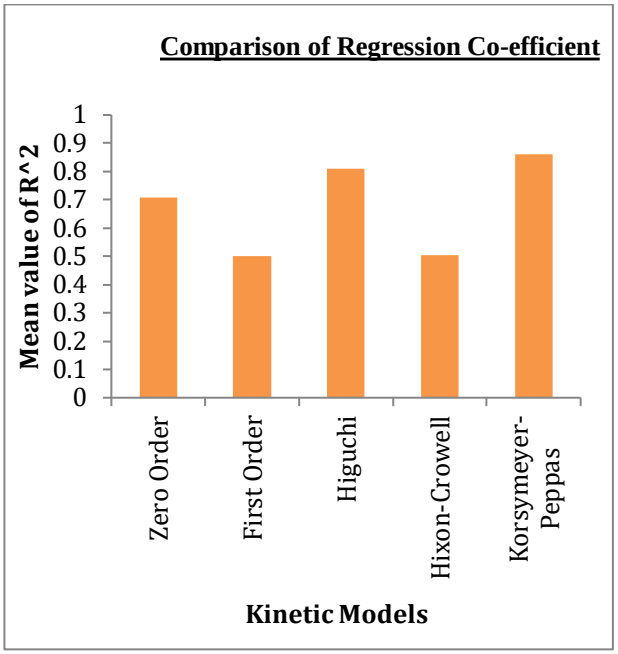

Figure 8: Comparison of Regression co-efficient

the release kinetics pattern of F1 formulation detected mostly as diffusion-controlled. Increasing values in drug release represents the gradual dissolution and diffusion of Vildagliptin from microspheres. Formulation F1 revealed a high rise of release about 88.17 % (after 3.5 hours) and Formulation F5 showed the lowest value in drug release after 3.5 hours that is 44.49 %. Therefore, there is a possibility of prolonged drug release for F5 over an extended time period.

Drug Release Kinetics report

Drug Release kinetics study showed significant report for F1 Formulation with better release kinetics among other formulations. All six formulations mostly followed Korsmeyer-Peppas model and Higuchi model. Study explained that F1 formulation had highest Regression coefficient (R^2)values for Korsmeyer-Peppas and Higuchi model with values 0.977 and0.930 simultaneously Table 4, Figure 7. Korsmeyer-Peppas and Higuchi model represents diffusion controlled mechanism from microspheres. Figure 8 showed Comparison of Regression co-efficient.

CONLUSION

Current investigation aimed to prepare and evaluate Vildagliptin Microspheres (F1-F6) for detection of its potentiality against hyperglycaemia and reduction of multiple dosing. All six formulations of were estimated for analysis of average particle size, percentage of yield, swelling index, efficiency of drug entrapment, Drug release study (*In Vitro*) and Drug release kinetics. Overall study shows that particle size (average) of microspheres was ranges within 0.7 to 1.1 mm, from previous studies it was already proven that particle sizes were almost within accurate range. High-rise drug entrapment efficiency with smallest particle size was reported by Formulation F5. Giant value of swelling index and towering percentage yield (88.17%) were noticed by F2 and F6 respectively. According to the drug release study and drug release kinetics, most promising result was shown by Formulation F1. As per release kinetics and regression values it was concluded that F1 Formulation best among other formulations and gave better drug release pattern with diffusion controlled release from entrapped drug.

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