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DESIGN DEVELOPMENT AND EVALUATION OF MICROSPHERES CONTAINING GLIPIZIDE DRUG

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ABSTRACT

Microspheres can be employed to deliver medication in a rate-controlled and sometimes targeted manner. Medication is released from a microsphere by drug leaching from the polymer or by degradation of the polymer matrix. The purpose of this research was to formulate and system-antically evaluate in vitro performances of microspheres containing glipizide. The % yield of the microspheres significantly increased ($p < 0.05$) with increasing amount of carriers, which may be due to large amount of the polymers available to form a completely drug loaded microspheres. In terms of % yield, it can be concluded that microspheres prepared with chitosan and eudragit RS100 showed highest values as compared to microspheres prepared with carragenan and eudragit RLPO. Good uniformity in drug encapsulation was found among different batches of the formulations but it had been seen that capabilities of encapsulation efficiency of MCH and MRS were greater as compared to the MCR and MRL formulations. The encapsulation efficiency of the microspheres significantly increased ($p < 0.05$) with increasing amount of eudragit polymer. From the release data it was revealed that the entire tablet formulations were released above 90% of glipizide within 12 hrs. The release profile of TFMRS2 portrait that the faster release of glipizide was happened as compared to other formulations.

KEYWORDS: Microsphere, Glipizide, Chitosan, Eudragit, Release Rate, Solubility.

INTRODUCTION

Microsphere are free flowing solid particle made up of biodegradable and non-biodegradable material, ideally having a particle size less than 200 µm and can be injected by an 18 or 20 number needle. Microsphere eases sustained drug release and also reduces or eliminates gastrointestinal tract irritation. Microsphere is used to alter the drug release. Drug

absorption and side effects due to irritating drugs against the gastrointestinal mucosa is improved because microsphere are made up of small particle size less than 200 µm, which are widely distributed throughout the gastrointestinal tract.

Microspheres or microcapsules are multi-particulate systems, preferred over the conventional dosage forms like tablet and capsule because of their increased surface area, thus increasing the absorption of the drug, reducing the dosing frequency, and improving the patient compliance. Irritation commonly associated with topical therapies is one of the most significant factors contributing to lack of adherence and therefore therapeutic withdrawal. The local application-site reactions may be linked to components of the formulation and/or to the active drug itself. Microspheres are formed through a quasi-emulsion solvent diffusion method. Conventionally, an organic internal phase consisting of drug, ethyl alcohol, polymer, and triethyl citrate (TEC)/trichloromethane is introduced to an external phase of distilled water and polyvinyl alcohol (PVA) that is allowed to emulsify and then is continuously stirred for two hours. This mixture is then filtered to obtain the microspheres. Another way of synthesizing microspheres is free radical suspension polymerization, solvent evaporation, ion gelation techniques. Particle size, pore structure, diameter, volume, and release characteristics of the microspheres will determine the functional parameters. Particle size itself may influence the release rate of the active drug from the microsphere. The larger the particle size, the faster the release rate. In addition to enhanced tolerability, microsphere formulations provide the benefit of improved drug stability.

The range of techniques for the preparation of microspheres provides multiple options to control as drug administration aspects and to enhance the therapeutic efficacy of a given the drug. These delivery systems offer numerous advantages compared to conventional dosage forms, which include improved efficacy, reduced toxicity, improved patient compliance and convenience. Such systems often use macromolecules as carriers for the drugs. Microsphere plays an important role to improve bioavailability of conventional drugs and minimizing side effects.

Ideal characteristics of microspheres

- The ability to incorporate reasonably high concentrations of the drug.
- Stability of the preparation after synthesis with a clinically acceptable shelf life.
- Controlled particle size and dispersability in aqueous vehicles for injection.
- Release of active reagent with a good control over a wide time scale.
- Biocompatibility with a controllable biodegradability.
- Susceptibility to chemical modification.

Glipizide, a second-generation sulfonylurea, is used with diet to lower blood glucose in patients with diabetes mellitus type II. The primary mode of action of glipizide in experimental animals appears to be the stimulation of insulin secretion from the beta cells of pancreatic islet tissue and is thus dependent on functioning beta cells in the pancreatic islets.

In humans glipizide appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. In man, stimulation of insulin secretion by glipizide in response to a meal is undoubtedly of major importance. Fasting insulin levels are not elevated even on long-term glipizide administration, but the postprandial insulin response continues to be enhanced after at least 6 months of treatment. Some patients fail to respond initially, or gradually lose their responsiveness to sulfonylurea drugs, including glipizide.

The main mechanism of glipizide is Sulfonylureas likely bind to ATP-sensitive potassium-channel receptors on the pancreatic cell surface, reducing potassium conductance and causing depolarization of the membrane. Depolarization stimulates calcium ion influx through voltage-sensitive calcium channels, raising intracellular concentrations of calcium ions, which induces the secretion, or exocytosis, of insulin.

MATERIAL AND METHOD

Glipizide was collected as a gift sample from Supra Chemicals, Mumbai, India, was identified and characterized for the physico-chemical properties.

Carrageenan was procured from Merck Ltd, Mumbai, India, Chitosan was procured from India Sea Food, Cochin and Eudragit RS100 & RLPO were procured from Rohm Pharma, West Germany.

DESIGN AND DEVELOPMENT OF GLIPIZIDE MICROSPHERE BY USING CARRAGEENAN

Table 1: Compositions of various formulations of glipizide microspheres prepare with carrageenan along with their amount.

Sl. No.	Ingredients	Contents of various formulations				
		MCR1	MCR2	MCR3	MCR4	MCR5
1	**Glipizide (gm)**	1	1	1	1	1
2	**Carrageenan (% w/v)**	1	2	3	4	5
3	**KCl (% w/v)**	3	3	3	3	3
7	**Span 80 (% v/v)**	2	2	2	2	2
8	**Liquid paraffin oil**	Up to 200 ml	Up to 200 ml	Up to 200 ml	Up to 200 ml	Up to 200 ml

DESIGN AND DEVELOPMENT OF GLIPIZIDE MICROSPHERE BY USING CHITOSAN

Table 2: Compositions of various formulations of glipizide microspheres prepare with chitosan along with their amount.

Sl. No.	Ingredients	Contents of various formulations				
		MCH1	MCH2	MCH3	MCH4	MCH5
1	**Glipizide (gm)**	1	1	1	1	1
2	**Chitosan**	1	2	4	6	8
3	**Aqueous acetic acid (%v/v)**	2	2	2	2	2
5	**Gluteraldehyde (%v/v)**	25	25	25	25	25
6	**DCM (ml)**	6	6	6	6	6
7	**Span 80 (% v/v)**	0.5	0.5	0.5	0.5	0.5
8	**Liquid paraffin oil**	Upto 100 ml	Upto 100 ml	Upto 100 ml	Upto 100 ml	Upto 100 ml

DESIGN AND DEVELOPMENT OF GLIPIZIDE MICROSPHERE BY USING EUDRAGIT RS 100/RLPO

Table 3: Compositions of various formulations of glipizide microspheres prepare with eudragit RS100/RLPO along with their amount

Sl. No.	Ingredients	Contents of various formulations				
		MRS1/MRL1	MRS2/MRL2	MRS3/MRL3	MRS4/MRL4	MRS5/MRL5
1	**Glipizide (gm)**	1	1	1	1	1
2	**Eudragit RS100/RLPO (gm)**	0.05	1	2	3	4
3	**Ethanol (ml)**	6	6	6	6	6
5	**DCM (ml)**	6	6	6	6	6
6	**Span 80 (% w/v)**	1	1	1	1	1
7	**Liquid paraffin oil**	Upto 100 ml	Upto 100 ml	Upto 100 ml	Upto 100 ml	Upto 100 ml

DESIGN, DEVELOPMENT AND EVALUATION OF PREPARED TABLETS FORMULATIONS:

FORMULATION & EVALUATION OF GLIPIZIDE TABLETS BY USING PREPARED BEST MICROSPHERES

METHODS

FORMULATION OF GLIPIZIDE TABLETS OF BEST SELECTED MICROSPHERES

On the basis of drug release pattern, % yield and drug entrapment efficiency, best microspheres were selected to prepare tablets formulations. Microspheres MCR5 and MRS5 contained carrageenan and eudragit RS 100, respectively were considered respectively. The composition of glipizide tablet formulations is presented in **Table 4**. Lactose and microcrystalline cellulose were used as diluents and disintegrating agent, respectively. The amount of microcrystalline cellulose and lactose were varied in different formulations. Accurately weighted amount of microspheres containing glipizide equivalent to 1 gm was taken in a glass mortar and then all the excipents magnesium stearate and talc were blended with the help of a pastel for 30 min. these mixtures was blended with magnesium stearate and talc in polyethylene bag for 10 min. The lubricated microspheres obtained were compressed by a single punch-tabletting machine (Kilburns, Allahabad, India) under constant pressure using 13 mm punch.

Table 4: Composition of each glipizide tablet containing microspheres.

Formulation code	**TFMCH1**	**TFMCH1**	**TFMRS1**	**TFMRS2**
Microspheres	**MCH4**	**MCH4**	**MRS4**	**MRS4**
	equivalent to 50 mg glipizide=260mg			
Excipients taken (mg)				
Microcrystalline cellulose	70	100	70	100
Starch	21	21	21	21
Lactose	140	110	140	110
Magnesium stearate	5	5	5	5
Talc	4	4	4	4
Total	500	500	500	500

*The amount of all excipients were expressed in mg; ** means tablets formulations prepared with; ǂ means tablets formulations prepared with.

EVALUATION OF COMPRESSED TABLETS

Shape of tablets

The shape of compressed tablets was examined under the magnifying lens.

Weight variation test

The weight variation test of tablets of all formulations batches were carried out by randomly selecting twenty tablets from each formulation and weight of twenty tablets was determined. The average weight of individual tablet was calculated. Then individual tablets were weighed and the individual weight was compared with an average weight.

Assay of tablets

Twenty tablets of each formulation were placed in a mortar and powdered with pestle. An amount equivalent to 50 mg of glipizide was taken in a volumetric flask and shaken with 50 ml of methanol and diluted to 100 ml with water. The solution was filtered through a membrane filter (0.22 µm). One milliliter of the filtrate was withdrawn and suitably diluted to 100 ml with 0.1 (N) HCl. The absorbance of the solution was measured using UV-Visible spectrophotometer (UV-1700, Pharmaspec, Shimadzu, Tokyo, Japan). The content uniformity test of each formulation was carried out in triplicate.

Hardness test

The hardness of three randomly selected tablets from each formulation was determined using Monsanto hardness tester (Monsento, Mumbai, India). Hardness of tablets was expressed in kg/cm^2.

Friability test

The friability test of tablets of each formulation were carried out in triplicate by taking ten tablets from each formulation and weighed. The tablets were placed in Roche friabilator (Labotech, Mumbai, India) and operated at 25 rpm for 4 minutes or run up to 100 revolutions by dropping the tablets through a distance of 6″ with each revolution. The tablets were then dedusted and reweighed. The friability was calculated as the percent weight loss of ten tablets.

The friability formula is given as:

$\% F=(1-W_0)/W \times 100$ …….eq.5.10

Where,

F is friability,

W_0 is the weight of tablets before test,

W is weight of tablets after test.

Thickness of tablets

Thickness and diameter were measured using a calibrated dial caliper (Mitutoya Corporation, Japan). Three tablets of each formulation were taken randomly and thickness was measured individually.

Dissolution studies

In vitro release study of tablet (n = 6) of each formulation was carried out using USP XXIII paddle dissolution test apparatus (Electro Lab Dissolution Tester (TDT-08L) at 100 rpm. The release study was performed in 900 ml simulated gastric fluid (0.1N HCl, pH 1.2) for 2hrs and phosphate buffer solution at pH 6.8 for next 10 hrs, by changing the dissolution media and the temperature of the release media was maintained at 37 ± 0.5^oC. Samples (1 ml) were withdrawn at predetermined intervals and replaced with equivalent volume of fresh medium. The samples were filtered through Whatman filter paper and analyzed the drug content after appropriate dilution by UV-Visible spectrophotometer (UV-1700, Pharmaspec, Shimadzu, Tokyo, Japan).

Data analysis

Results are expressed as mean values and the significance of the difference observed was analyzed by the Student's t-test. In all tests, a probability value of $p < 0.05$ was considered statistically significant.

STABILITY STUDIES OF BEST SELECTED TABLET FORMULATIONS AS PER ICH GUIDELINES

AIM

Stability of a pharmaceutical preparation can be defined as "the capability of a particular formulation (dosage form or drug product) in a specific container and closer system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications throughout its self life" [8, 186 & 208]. The stability of a product can be evaluated if its degradation impurities, it's assay, its dissolution and disintegration time does not generate/alter considerably after 6 months of accelerated stability testing at 40°C and 75% RH as per the ICH guidelines.

Among the different tablet formulations, formulation **TFMRS2** showed highest released of glipizide (released approximately 96% drug within 12hrs). Therefore, formulation **TFMRS2** was selected for further studies.

METHODS

Stress conditions

Stability study of formulation **TFMRS2** was carried out under the different stress conditions and the method was followed as earlier mentioned by some researchers [8, 186 & 208]. Formulation **TFMRS2** was stored at 40°C with 75 ± 5% RH in Stability Chambers (Newtronics Pvt. Ltd). After 30, 60 and 90 days all the quality control tests of tablet including drug contents of that formulation were determined. *In vitro* release study was also carried out for the same formulation after stipulated time period of time intervals. Methods followed for all the quality control tests were discussed in earlier section. The drug content of the tablet was determined spectrophotometrically using UV-vis spectrophotometer at regular intervals of 0, 30, 60 and 90 days.

RESULT AND DISCUSSION

PREFORMUATION STUDIES: CHARACTERIZATION OF DRUG

Melting point of Glipizide was found to be in the range 201-203°C, which fully complied with earlier reported values.

Fourier Transform Infrared Spectroscopy (FTIR) Analysis

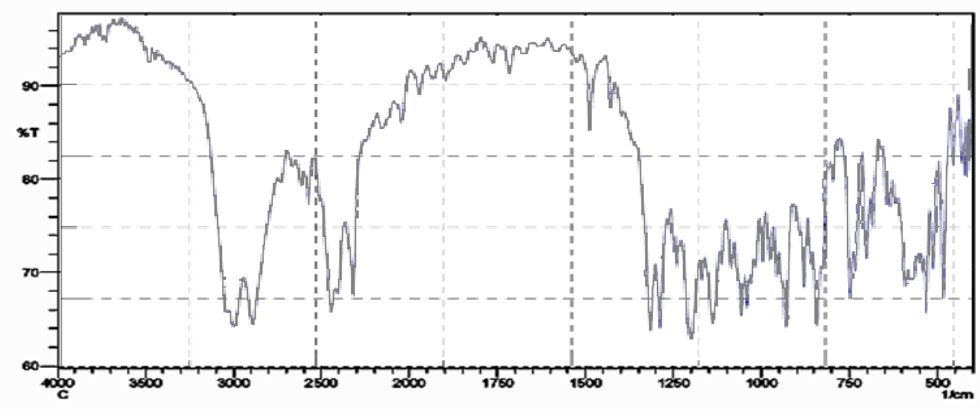


Fig. 1: FTIR spectrum of Glipizide.

FTIR Spectra of Glipizide

FUNCTIONAL GROUP	OBSERVED VALUE (cm^{-1})
N-H amide	3324.34 cm^{-1}
C-H aromatic stretching	2943.67 cm^{-1}
C-H aliphatic stretching	2854.76 cm-1
C=C stretch	1524.72 cm-1
C=O	1687.29 cm^{-1}
C=N	1330.86 cm^{-1}
C-H bending	1530.66 cm-1
SO_2	1158.54 cm-1

Differential Scanning Calorimetry

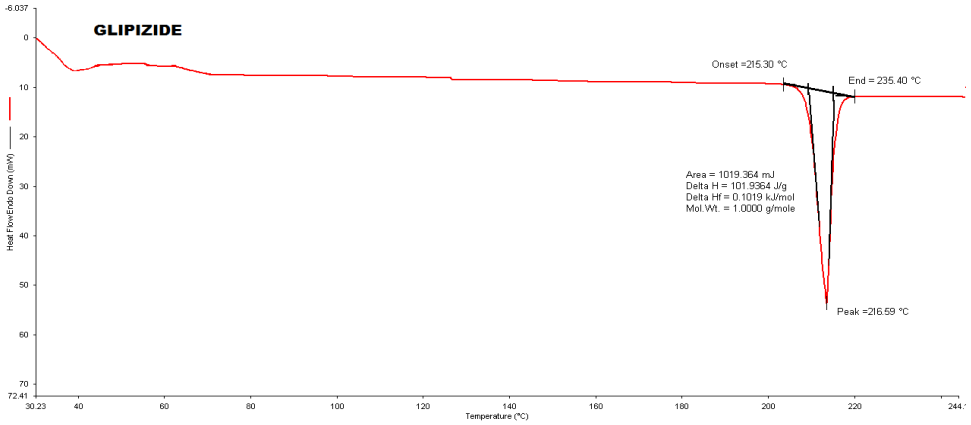


Fig. 2: DSC thermogram of Glipizide.

PREPARATION OF MICROPHERES

CHARACTERIZATION OF FORMULATIONS BY FTIR, DSC AND XRD METHOD- FT-IR SPECTROSCOPY

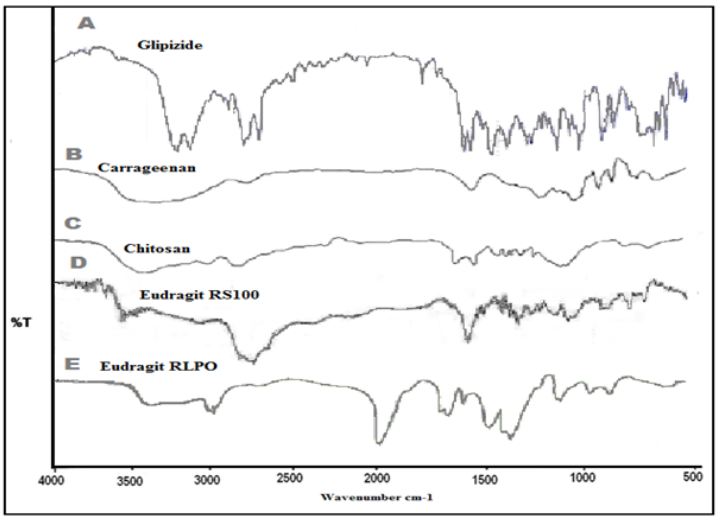


Fig. 3: FTIR spectra of A: glipizide, B: carrageenan, C: chitosan, D: eudragit RS100 and E: eudragit RLPO.

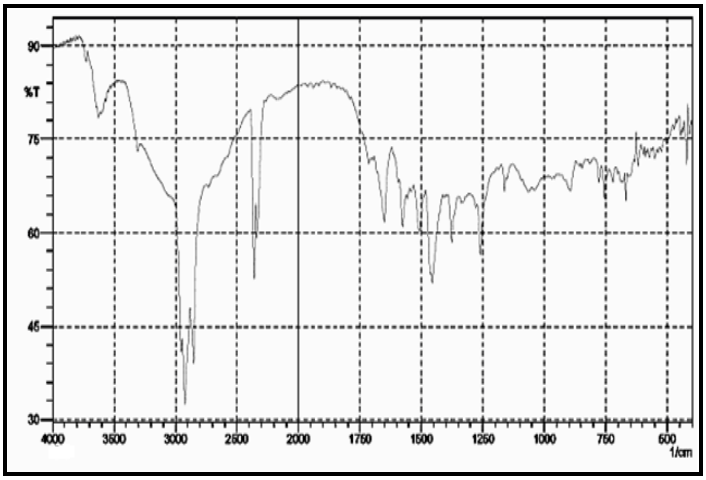


Fig. 4: FTIR spectra drug loaded microspheres of carrageenan [MCR3].

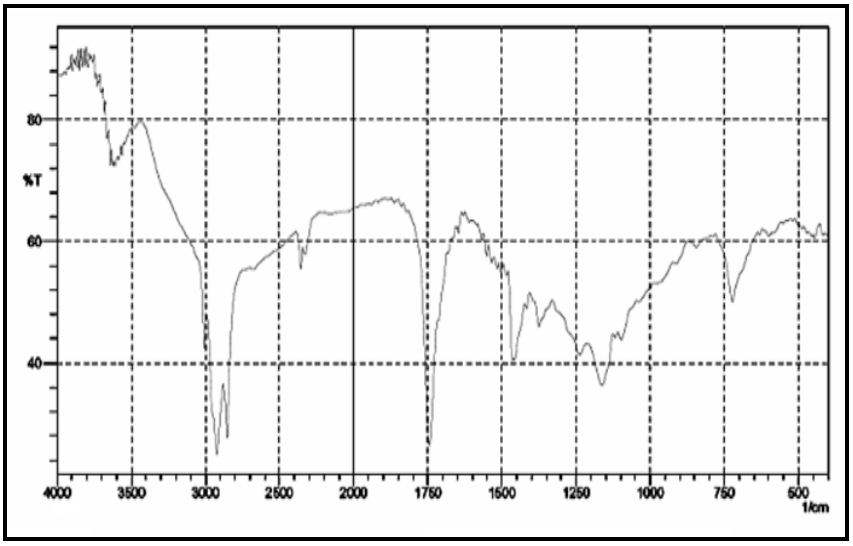


Fig. 5: FTIR spectra of chitosan and drug loaded microspheres [MCH4].

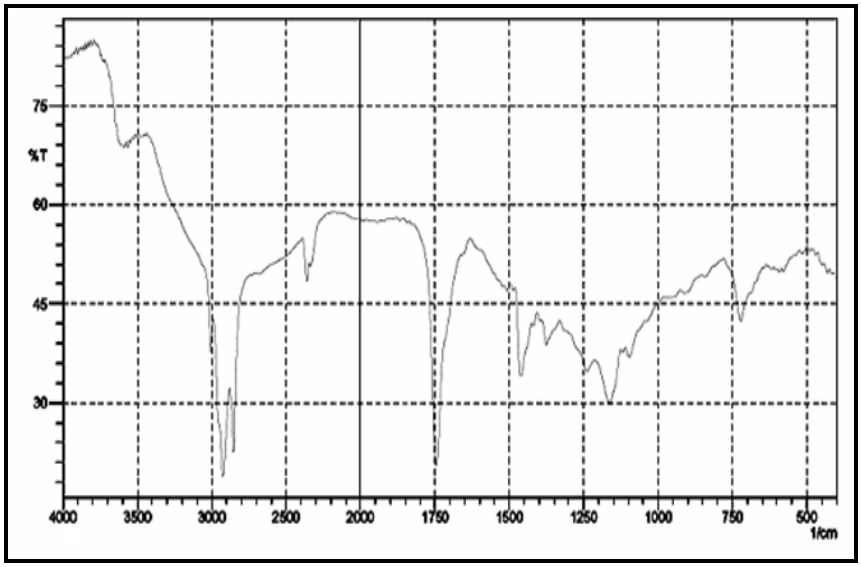


Fig. 6: FTIR spectra of eudragit RS100 and drug loaded microspheres [MRS4].

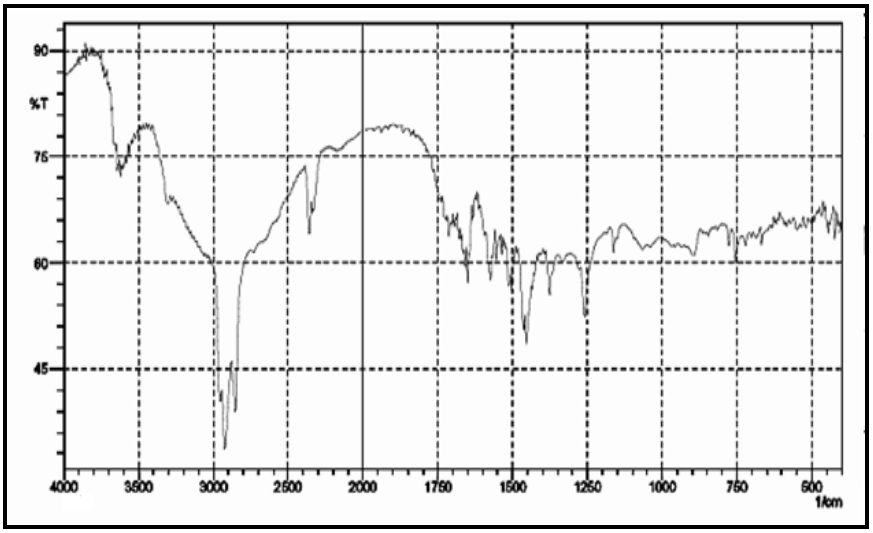
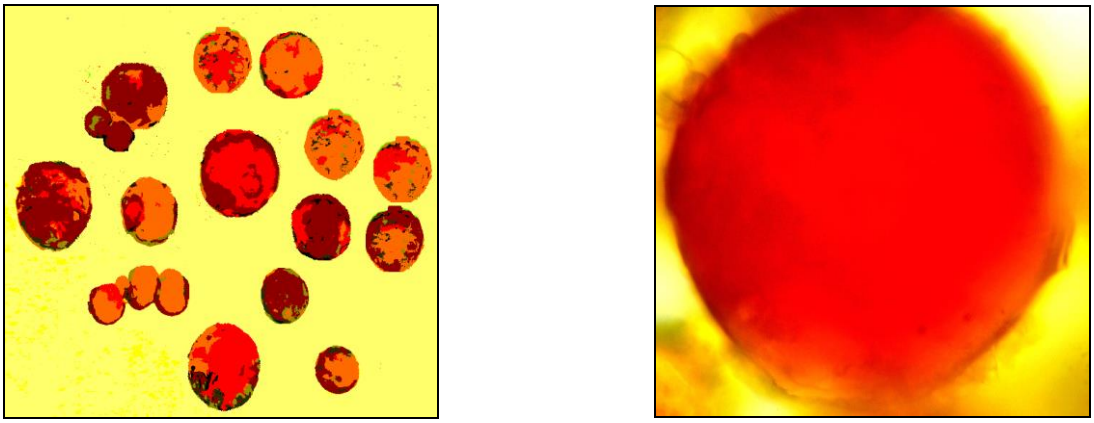


Fig. 7: FTIR spectra of eudragit RLPO and drug loaded microspheres [MRL3].

EVALUATIONS OF MICROSPHERES

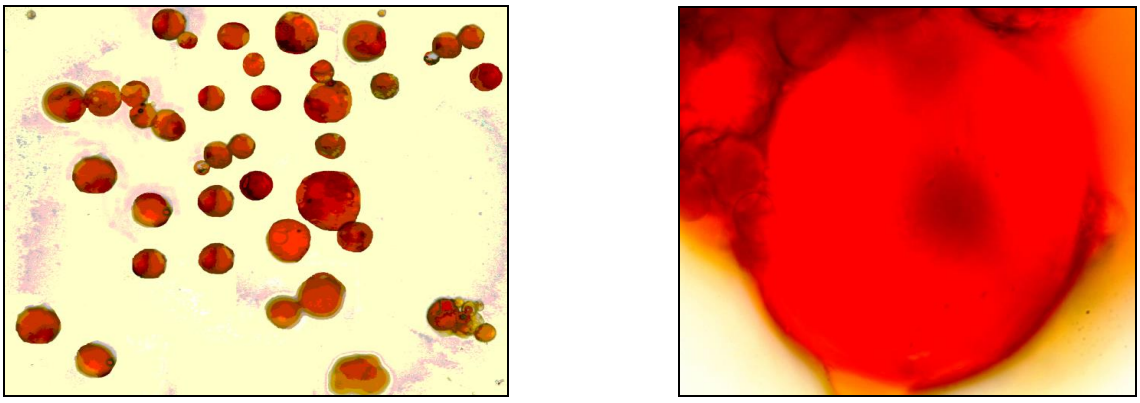
STUDY OF SURFACE MORPHOLOGY:

BY CONVENTIONAL LIGHT MICROSCOPE



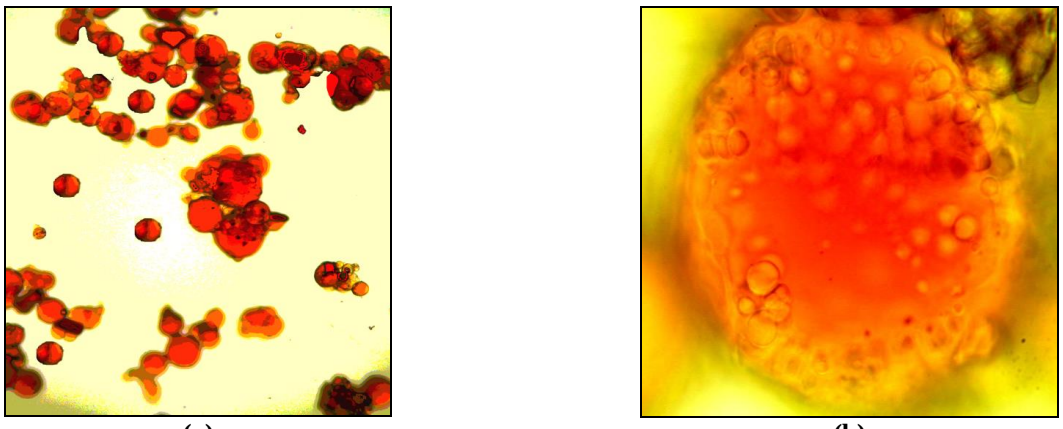
(a) (b)

Figure 8: Photomicrograph of microspheres prepared with glipizide & carrageenan [MCR3]. Resolution 4x (a) and 40x(b).



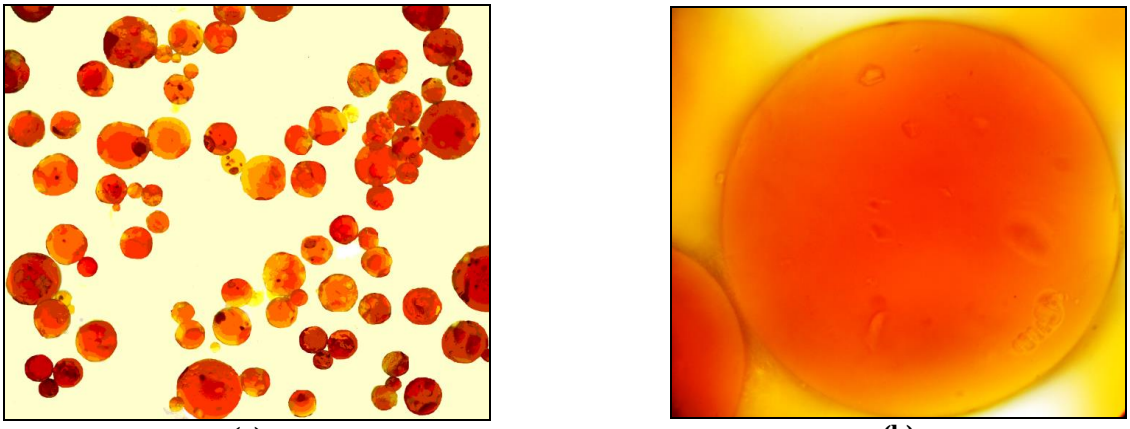
(a) (b)

Fig. 9: Photomicrograph of of microspheres prepared with glipizide & carrageenan [MCR5]. Resolution 4x (a) and 40x (b)



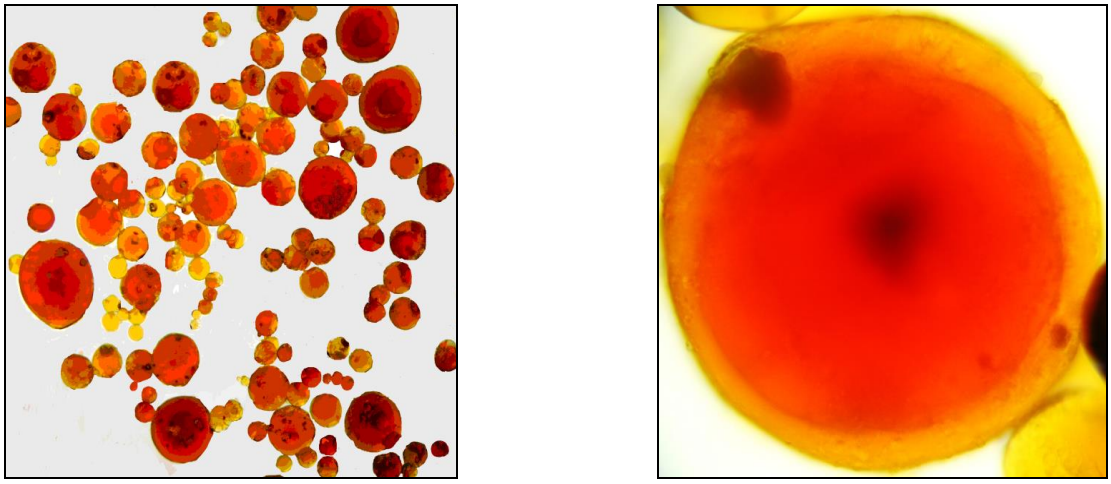
(a) (b)

Fig.10: Photomicrograph of microspheres prepared with glipizide & chitosan [MCH5]. Resolution 4x (a) and 40x(b).



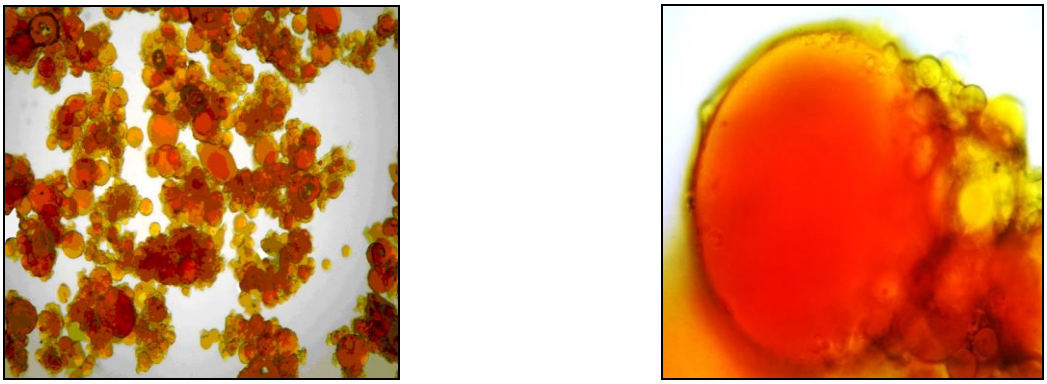
(a) (b)

Fig. 11: Photomicrograph of microspheres prepared with glipizide & chitosan [MCH4]. Resolution 4x (a) and 40x (b).



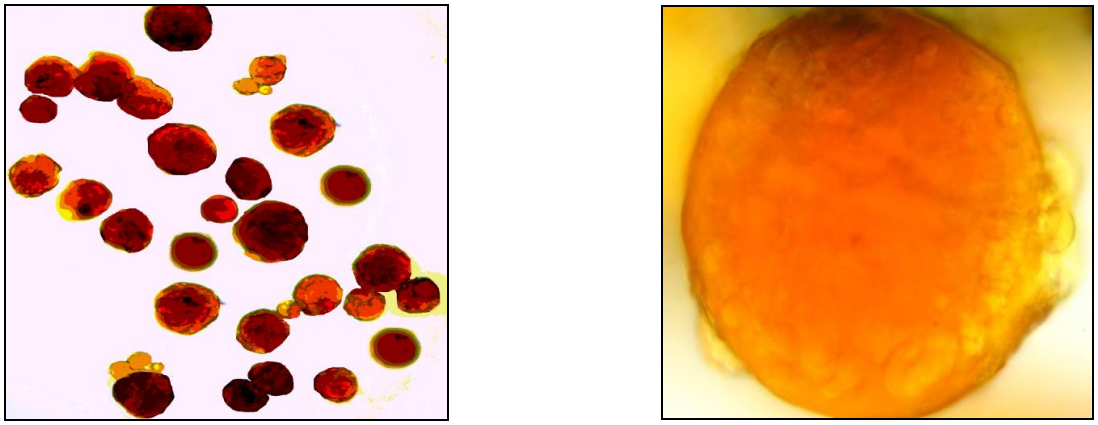
(a) (b)

Fig. 12: Photomicrograph of microspheres prepared with glipizide & eudragit RS 100 [MRS4]. Resolution 4x (a) and 40x (b).



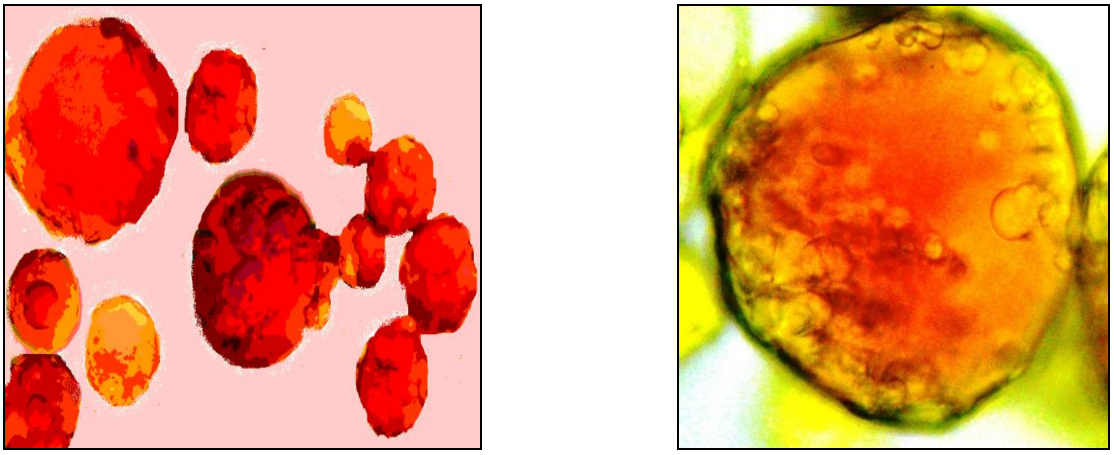
(a) (b)

Fig. 13: Photomicrograph of microspheres prepared with glipizide & eudragit RS 100 [MRS5]. Resolution 4x (a) and 40x (b).



(a) (b)

Fig. 14: Photomicrograph of microspheres prepared with glipizide & eudragit RLPO [MRL3]. Resolution 4x (a) and 40x (b).

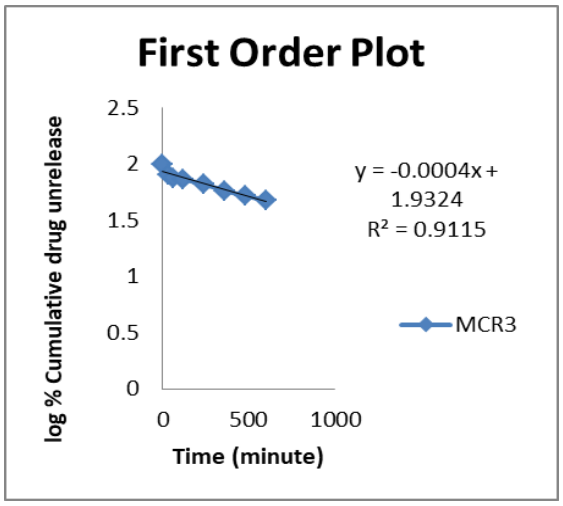


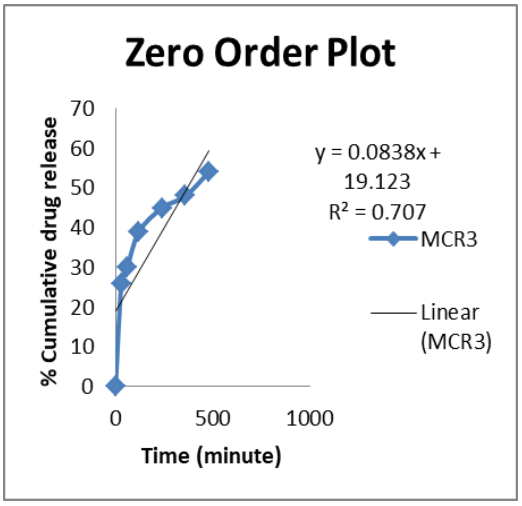
(a) (b)

Fig.15: Photomicrograph of microspheres prepared with glipizide & eudragit RLPO [MRL5]. Resolution 4x (a) and 40x (b).

Two dimensional photomicrographs of all the glipizide loaded microspheres were taken at 4X & 60X magnification resolution and which are represented in figures 6.35-6.42. It was observed that as we increased the amount of carriers correspondingly more variations of the sizes of the microsphers were also found.

***In vitro* release studies**





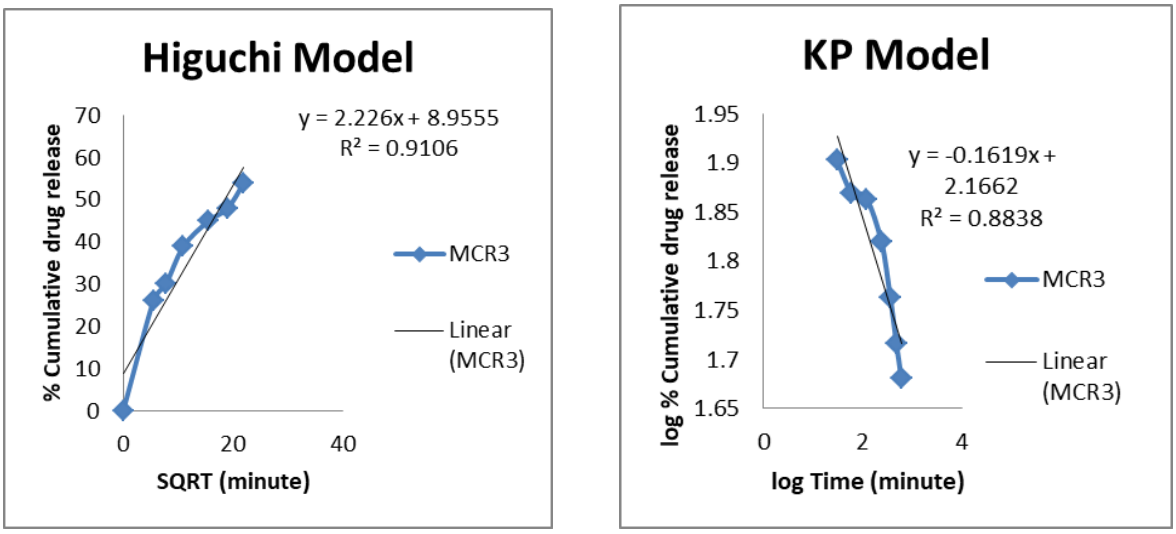


Figure 16: *In-vitro* drug release profiles of glipizide released from MCR3 microspheres prepared with carrageenan. Mean percentage release was considered for construction of release profile.

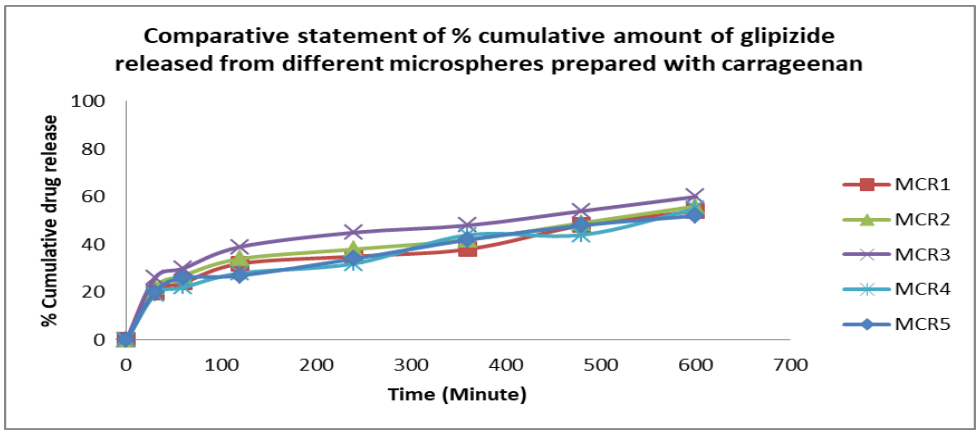
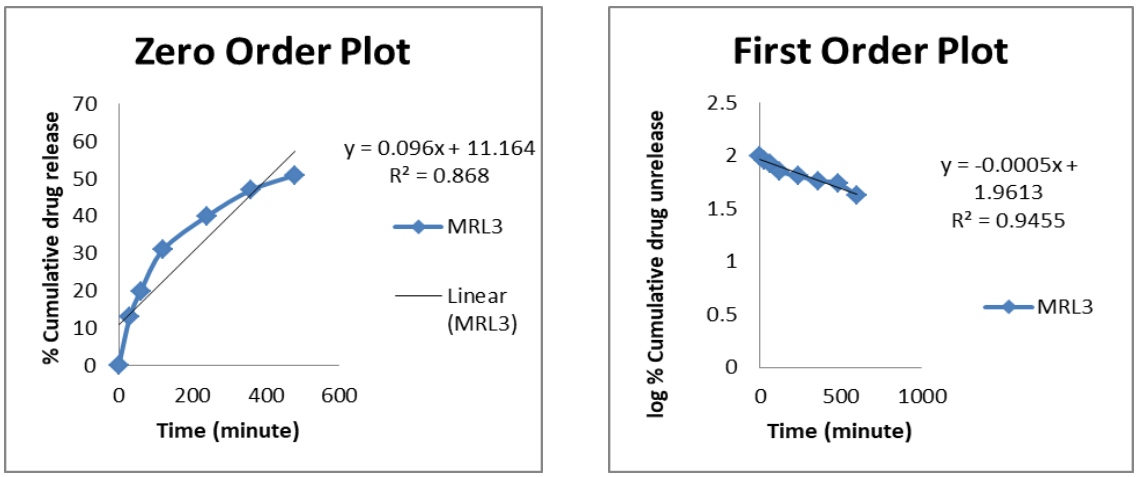


Figure 17: *In-vitro* drug release profiles of glipizide released from different microspheres prepared with carrageenan. Mean percentage release was considered for construction of release profile (n = 3).

Time to release 90% ($t_{90\%}$) of glipizide released from different microspheres prepared with eudragit RLPO.

Code	MRL1	MRL2	MRL3	MRL4	MRL5
$t_{90\%\ (min)}$	805	837	818	1088	957



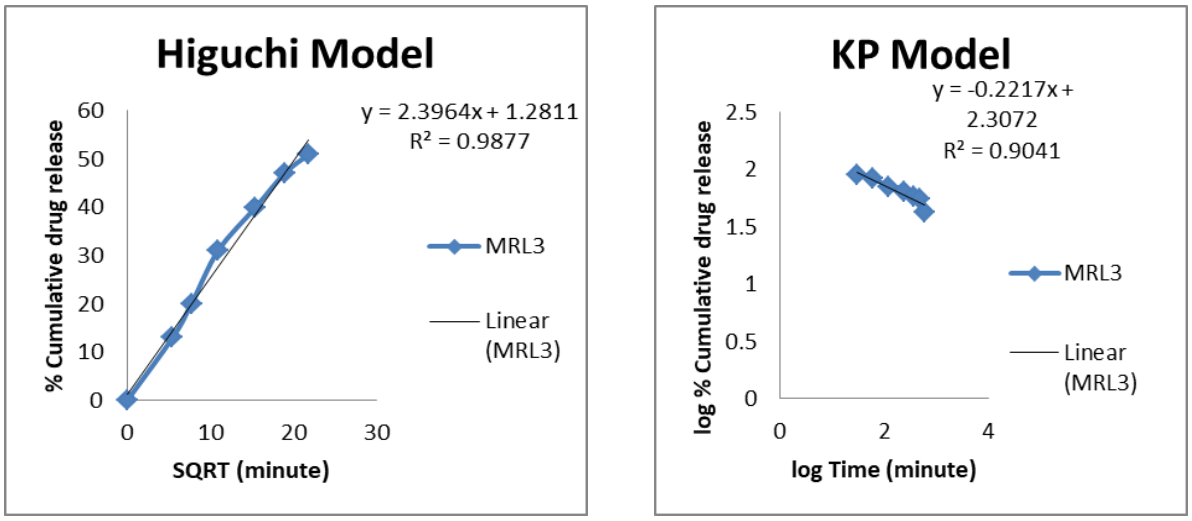


Figure 18: *In-vitro* drug release profiles of glipizide released from MRL3 microspheres prepared with eudragit RLPO. Mean percentage release was considered for construction of release profile (n = 3).

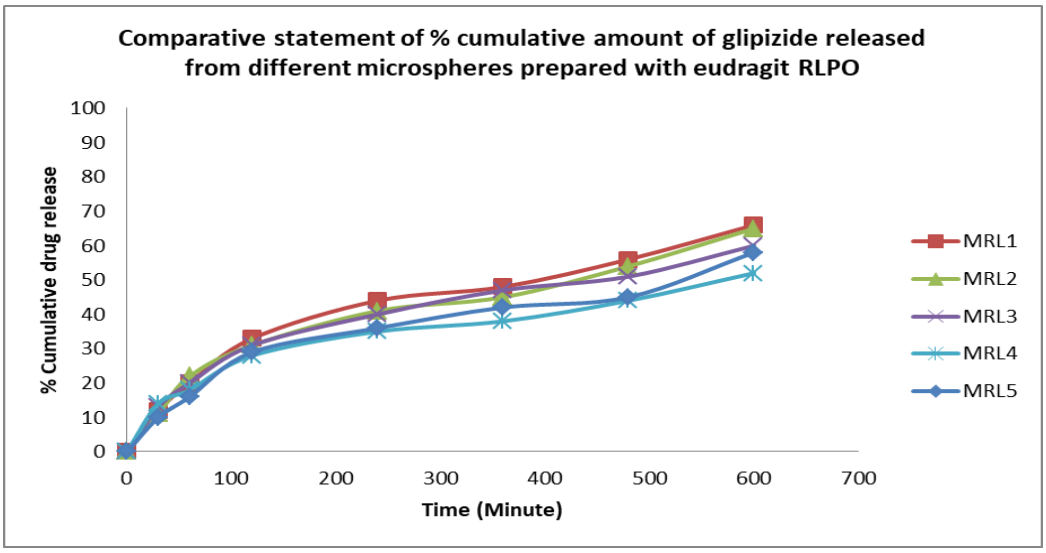


Figure 19: *In-vitro* drug release profiles of glipizide released from different microspheres prepared with eudragit RLPO. Mean percentage release was considered for construction of release profile (n = 3).

CONCLUSION

The release of glipizide from all the tablets formulation followed mixed order kinetic. The high value of R^2 in Higuchi model of TFMRS2 revealed that the release of glipizide from all the formulations followed diffusion controlled. The release data when fitted to the Korsmeyer-Peppas model it was found that formulations TFMRS2 followed this model and diffusion exponent was found less than 0.184 indicating the release of glipizide from the tablet followed Fickian transport. But the high R^2 value of Korsmeyer-Peppas model clearly indicated the release mechanism of glipizide from different tablets formulation were strongly dependent on model. The *in vitro* release data of tablet formulation at initial stage was considered as the reference for release study. The *in vitro* release profile revealed that the release profile after 6 months of storage at accelerated condition was found to be similar to that of reference one. Based on the results it was confirmed that the tablet was stable after 6 months of storage at accelerated stability conditions, probably due to the

fact that the stable excipients used to prepare the tablets, but further real time stability analysis is required to establish the stability and to determine the shelf life of the best selected formulation.

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