International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Formulation and Characterization of Blend Microspheres of Anti Diabetic Drug Glimepiride

Ashif Ali Mansoori

Master of Pharmacy Pharmaceutics Bhabha Pharmacy Research Institute Bhopal MP

Abstract

The objective of the present investigation was to prepare polymeric blend microspheres of glimepiride for improving its half-life using chitosan and gelatin as the two polymers for preparing the blend. The blend microspheres of chitosan and gelatin were prepared by using different ratios of both the polymers as well as cross-linking agent, glutaraldehyde (GA), by emulsion cross-linking method.

The optimum formulation was one which exhibited the lowest particles size and it was used to load glimepiride (20% by weight) of the polymers. The glimepiride loaded blend microspheres were evaluated for yield, drug polymer interaction, entrapment efficiency, surface study and *in vitro* release.

The particle size of the blend microspheres was found to be in the range of 126.8 µm to 371.3 µm. The lowest particle size (126.8 ± 6.11 µm) was obtained in AF5 containing 50% of gelatin and 50% of chitosan.

The FTIR spectra of the physical mixture of glimepiride, gelatin and chitosan displayed all the characteristic peaks of glimepiride, thus indicating that no incompatibility was present between the drug and the polymer.

The SEM image of the drug loaded blend microsphere revealed spherical particles of irregular size with smooth surface.

The average particles size of the glimepiride loaded blend microspheres was obtained to be 131.4 ± 9.7 µm with a yield of 91.6% by weight of the drug and polymers used for formulation of the microspheres.

It was found that 82.4 ± 6.8% of glimepiride was found to be entrapped in the particles.

The results of the *in vitro* release studies of the glimepiride loaded blend microsphere revealed that 71.49 ± 0.74 % glimepiride was released from the particles at the end of 12th hour of study.

Keywords: glimepiride,blend microspheres,glutaraldehyde

1. Introduction

1.1 Microspheres and Controlled Release

Some of the drawbacks of traditional therapy can be resolved, and the therapeutic effectiveness of a specific drug can be improved, with the help of a well-designed controlled drug delivery system. The drug must be delivered to the target tissue in the ideal quantity and at the proper time in order to cause the least amount of toxicity and adverse effects and achieve the greatest therapeutic efficacy[1]. In order to deliver a medicinal chemical to the target region with a continuous regulated release, there are several different methods. Using microspheres as medication carriers is one such strategy. Microspheres are typically free-flowing powders made of biodegradable proteins or synthetic polymers, with a preferred particle size of less than 200 m[2].

Polymers are frequently utilised as microspheres. They are divided into two categories:

1. Artificial Polymers
2. Organic polymers

There are two categories of synthetic polymers.

a. Polymers that are not biodegradable, such as Poly methyl methacrylate (PMMA),Glycidyl methacrylate,[3] Acrolein[4], Epoxy plastics

b. Biodegradable materials, such as lactides, glycolides, and their co-polymers[5] Poly anhydrides and Poly alkyl cyano acrylates

2. Natural polymers derived from several sources, including proteins, carbohydrates, and carbohydrates that have undergone chemical modification

Proteins: Albumin[6] , Gelatin[7] , and Collagen

Carbohydrates: Agarose, Carrageenan, Chitosan, Starch[8]

Chemically modified carbohydrates: Poly dextran, Poly starch.

When delivered parenterally, non-biodegradable drug carriers have the potential to cause long-term carrier toxicity because they stay in the body after the drug has been fully released.

Parenteral applications are better suited for biodegradable carriers because they don't cause carrier toxicity and break down in the body to non-toxic breakdown products[1].

1.1.1 Loading of drug and its release kinetics

Two main techniques are used to load the active components onto the microspheres: either during the creation of the microspheres or after their synthesis by incubating them with the medication or protein. Physical entrapment, chemical coupling, and surface adsorption are three different ways that the active component might be loaded. The composition of the drug or polymer (monomer if utilised) and the preparation technique have a significant impact on the degree of entrapment.

The drug can be mixed in at the time of preparation to achieve maximum loading, but other process variables, such as the mixing technique, the presence of additives (such as cross-linking agents and surfactant stabilisers), the polymerization temperature, the amount of agitation, etc., may also have an impact. In the case of microspheres, the release of the active ingredient is a crucial factor. The type of polymer employed in the preparation and the nature of the active medication both affect the release profile from the microspheres. The structure or micro-morphology of the carrier, as well as the characteristics of the polymer itself, have an impact on the drug release from both biodegradable and non-biodegradable microspheres.

Any one of the three methods—the osmotically driven burst mechanism, pore diffusion mechanism, or erosion or degradation of the polymer—could cause the medications to be released through the microspheres. Osmotically induced burst mechanisms cause the membrane to rupture by allowing water to infiltrate into the core through a biodegradable or non-biodegradable covering. The ratio of macromolecules to polymers, the size of the dispersed macromolecule's particles, and the size of the microspheres' particles all play major roles in determining the burst effect. Because the penetrating water front continues to disperse towards the core, the pore diffusion method is so termed. The accumulation of monomer in the release media occurs concurrently with polymer erosion, or the loss of polymer. As water seeps through the carrier, changing its microstructure and causing the matrix to become plastic, the polymer begins to erode.

It is possible to comprehend drug release from non-biodegradable polymers by taking into account the shape of the carrier. The overall release profile of the medication or active ingredients is determined by the geometry of the carrier, i.e. whether it is reservoir type, where the drug is present as the core, or matrix type, where the drug is spread throughout the carrier.

1.1.2 Methods of Preparation[9]

The creation of microspheres needs to meet specific requirements:

1. The ability to incorporate reasonably high concentrations of the drug.
2. Stability of the preparation after synthesis with a clinically acceptable shelf life.
3. Controlled particle size and dispersability in aqueous vehicles for injection.
4. Controlled release of the active reagent over a broad time frame.
5. Biodegradability that can be controlled, as well as
6. Chemical modification sensitivity.

1.1.2.1 Single emulsion method

The single emulsion technique is used to create the micro particle carriers for natural polymers, such as proteins and carbohydrates. After being dissolved or dispersed in an aqueous media, the natural polymers are then distributed in a non-aqueous medium, such as oil. The dispersed globule is then cross-linked after that. Either heat or chemical cross linkers can be used to achieve the cross linking. Glutaraldehyde, formaldehyde, di acid chloride, and other chemicals are utilised as cross-linking agents. Thermolabile compounds are not appropriate for heat denaturation. If an active component is applied during preparation and subsequently subjected to centrifugation, washing, or separation, chemical cross-linking has the drawback of exposing the active ingredient to excessive amounts of chemicals.

1.1.2.2 Double emulsion method

The ideal candidates for the double emulsion method of microsphere creation are water soluble medicines, peptides, proteins, and vaccines. It requires creating several emulsions or a double emulsion of type w/o/w. Both natural and artificial polymers can be employed using this technique. The lipophilic organic continuous phase contains a dispersion of the aqueous protein solution. The active ingredients could be present in this protein solution. The polymer solution that eventually wraps the protein present in the scattered aqueous phase makes up the continuous phase in most cases. The primary emulsion is then homogenised or sonicated before being added to the polyvinyl alcohol (PVA) aqueous solution. A double emulsion is created as a result of this. The next step is to remove the solvent from the emulsion, either using solvent extraction or solvent evaporation. Using the technique of double emulsion solvent evaporation/ extraction, a range of hydrophilic pharmaceuticals, including leutinizing hormone releasing hormone (LH-RH) agonist, vaccines, proteins/peptides, and conventional compounds are successfully incorporated into the microspheres.

1.1.2.3 Polymerization techniques

The traditional methods of polymerization for creating microspheres can be broadly divided into: I. Normal polymerization Interfacial polymerization, II. Both processes take place in the liquid phase.

1.1.2.4 Coacervation Phase separation method

This procedure is based on the idea that lowering the solubility of the polymer in organic phase will have an impact on how quickly coacervates, a phase rich in polymers, develop. In this approach, the polymer solution containing the drug particles is mixed with an incompatible polymer, causing the first polymer to phase separate and engulf the drug particles. The solidification of the polymer is caused by the addition of non-solvent. This technique was used to create polylactic acid (PLA) microspheres utilising butadiene as an incompatible polymer. The rate of creating the coacervates impacts the dispersion of the polymer film, the particle size, and the agglomeration of the produced particles, hence the process variables are crucial. Agglomeration must be prevented by vigorously swirling the suspension with a proper speed stirrer because as soon as the creation of microspheres starts, the polymerized globules begin to clump together and create agglomerates. Since there is no clearly defined state at which equilibrium is reached, the process variables are crucial since they regulate the kinetics of the produced particles.

1.1.2.5 Spray drying and spray setting

These techniques rely on the polymer and medication mist in the air drying. Spray drying and spray congealing are two different techniques that are distinguished by the elimination of the solvent or chilling of the solution, respectively. First, a suitable volatile organic solvent, such as acetone, dichloromethane, or another, is used to dissolve the polymer. The medication is subsequently dissolved in the polymer solution while being homogenised at high speed. Then, a jet of hot air is used to atomize this dispersion. The process of atomization produces tiny droplets or a fine mist, from which the solvent instantly evaporates, resulting in the creation of microspheres with a size range of 1 to 100 µm. The cyclone separator is used to separate microparticles from the hot air, and vacuum drying is used to remove any remaining solvent. The process's viability for use in aseptic environments is one of its main benefits.

1.1.2.6 Solvent abstraction

The process of making microparticles by solvent evaporation entails removing the organic phase by extracting the organic solvent. Organic solvents that are water soluble, like isopropanol, are used in the procedure. Extraction with water is used to get rid of the organic phase. The microspheres' hardening time is slashed by this procedure. Direct addition of the medication or protein to the organic polymer solution is one version of the procedure. The ratio of emulsion volume to water, water temperature, and the polymer's solubility profile all affect how quickly solvent is removed using the extraction procedure.

1.1.3 Physicochemical Evaluation[9]

1. Particle dimension and form
2. Electron spectroscopy for element examination
3. ATR FourierTransfom Infrared Spectroscopy
4. Density analysis
5. Isoelectric point
6. Surface carboxylic acid scum
7. Surface amino acid scum
8. Capture effectiveness

9. Angle of interaction
10. *In vitro* release methods
11. *In vivo* release methods

1.1.4 Advantages[9]

1. A reliable method to maintain the required concentration at the site of interest while delivering the drug to the target location with specificity, if adjusted.
2. Solid biodegradable microspheres have the ability to deliver drugs in a regulated manner over the entire particle matrix.
3. Microspheres attracted a lot of attention for their sustained release as well as their ability to direct anticancer medications to the tumour.
4. It has been discovered that the size, surface charge, and surface hydrophilicity of microspheres have a significant role in predicting the fate of particles in vivo.
5. Research on the uptake of microspheres by macrophages has shown that they can be used to deliver medications to infections that are intracellular.

1.2 Blend Microspheres

Over the past few decades, one of the main fields of polymer science research and development has been the technology of polymer blends. Polymer blends have the benefit of lower research and development costs as compared to creating a new polymeric structure. Additionally, blends provide property profile combinations that are difficult to come across in single polymers or new polymeric structures. These mixtures make fascinating raw materials for the creation of composite polymers, films, sponges, hydrogels, complexing agents, membranes, dressings, drug encapsulation shells, sutures, and membranes for sponges. Natural polymers like shellac have been used for binding things and as a hot wood varnish for centuries. The first polymer mix to be patented by Alexander Parkes was a combination of natural rubber and gutta percha. The type of bonds that bind the components together, their compatibility, and the characteristics that facilitate the formation of supramolecular structures all affect the physiochemical and mechanical aspects of such blends. There is increasing interest in this area, and several studies and analyses into the characteristics of polymer mix microspheres are becoming very significant in drug release. Microspheres allow for medication release control while reducing harmful side effects, eliminating the nuisance of frequent injections, and avoiding surgical procedures for both implantation and removal.

1.2.1 Polysaccharides Mixtures

Polysaccharide mixtures with both natural and artificial polymers make for fascinating materials. Blending solid polymers with solid polymers such as cellulose, chitin, and chitosan involves high pressure and shear deformation working together to effectively mix the reagents on a molecular level, which is necessary for the reaction to proceed. It is possible to prepare polymer compositions based on polysaccharides in a variety of ways. Similarities in cellulose, chitin, and chitosan structurally influence their compatibility and enable the creation of homogeneous blends.

The fundamental issue, however, is selecting the solvent for mix preparation. Bridgman anvils (1 to 50 GPa) that allow for the use of milligrammes of reactants or a twin screw pilot extruder (Berstorff, Germany) with heating control that offers pressures of 0.2 to 10 GPa and shear stresses of 0.3 to 3

M/mm2 were the two types of equipment employed. Analysis was done on the effects of mixing duration and chemical reaction passage on the kinetics and structure of the reaction.
The mechanical processing of the solid mixture of chitosan and cellulose led to a reduction in molecular mass, and the chemical reaction led to the development of branching and cross-linked structures. It was demonstrated that chitosan-cellulose

Abbreviation

SA	Sodium alginate
HPC	Hydroxypropyl cellulose
FTIR	Fourier transform infrared spectroscopy
DSC	Differential Scanning Calorimeters
TGA	Thermogravimetric analysis
SEM	Scanning electron microscopy
LCST	Lower critical solution temperature
HPC	Hydroxypropyl cellulose
MS	Mass spetrometry
PCL	Polycaprolactone
THB	The total hemoglobin
PLA-PCL	Poly lactic acid
AC	Activated carbon
MPS	Master production scheduling
QSM	Quality management system
MET	Metformin hydrochloride
OKG	Okra gum
GLG	Gallan gum
HPMC	Hydroxypropyl methylcellulose
XRD	X ray Diffraction
TH	Theophylline
DCM	Dichloromethane
PVA Solution	Polyvinyl alcohol
HEC	Hydroxyl ethyl cellulose
INH	Isoniazid is an antibiotic
FITC	Fluorescein isothiocyanate
BSA	Body surface area
MTT	Material transfer agreement
EC	Ethyl cellulose
PVP	Poly vinyl pyrrolidine
NFD	No fill detection
SOF	Sofosbuvir
PEO	Polyethylene oxide
PEG	Polyethylene glycol
PRD	Product requirements

2. Units

blends were more thoroughly ground when they were put through an extruder. As the degree of degradation increases, grinding chitosan and cellulose together causes a decrease in molecular mass and a rise in temperature. One H NMR spectroscopy-ray diffraction study of structural alterations revealed that sample treatment under more demanding conditions resulted in a nearly full amorphization of the product structure at the pressure of 1 GPa. With pressure and shear stress, there was a rise in the weak chemical interactions between two components as well as a change in the structure of hydrogen bonds. The blends were insoluble in both acidic and alkaline aqueous media as a result of the addition of a modest amount of cross-linking agents, which created three-dimensional structures with cross links.

The average particles size of the glimepiride loaded blend microspheres was obtained to be 131.4 ± 9.7 µm with a yield of 91.6% by weight of the drug and polymers used for formulation of the microspheres. It was found that 82.4 ± 6.8% of glimepiride was found to be entrapped in the particles. The results of the *in vitro* release studies of the glimepiride loaded blend microsphere revealed that 71.49 ± 0.74 % glimepiride was released from the particles at the end of 12th hour of study.

In the present investigation, an attempt was made to optimize polymeric blend microsphere using chitosan and gelatin and formulate glimepiride loaded blend microspheres for improving the half-life of glimepiride. The results obtained from the experimental study performed as per the protocols depicted in the previous chapter are presented in this chapter of the dissertation.

2.1 Preformulation Studies

2.1.1 Physical characterization of glimepiride

The color, odor, taste and appearance of the procured sample of glimepiride was observed using the sensory organs and the results were compared to the specifications (Table 6.1). The melting point and partition coefficient of glimepiride were also determined using standard procedures.

Table 2.1 Physical properties of glimepiride

S. No.	Property Studied	Specification[56]	Observation
1	Appearance	Powder	Sticky powder
2	Color	White	Off-white
3	Odor	Odorless	Odorless
4	Taste	Bitter	Bitter
5	Melting Temperature	207-209°C	210-211°C
6	Partition Coefficient (octanol-water)	3.81	3.74

2.1.2 Solubility summary of glimepiride

The solubility of glimepiride was qualitatively observed in water, methanol, ethanol, acetonitrile and dimethyl formamide (Table 6.2).

Table 2.2 Solubility of glimepiride

Solvent in which solubility was tested	Observation
Distilled Water	Insoluble
Methanol	Partially Soluble
Ethanol	Partially Soluble
Acetonitrile	Soluble
Dimethyl formamide	Soluble

2.1.3 UV absorption spectra of glimepiride

The absorption spectrum of glimepiride was obtained by dissolving the drug in methanol and scanning from 400 to 200 nm with the aid of a double beam UV Visible spectrophotometer (Figure 6.1). The absorption maxima was obtained to be 224.0 nm and was used to measuring the absorbance of glimepiride in solutions throughout the study. In previous studies the absorption maxima have been reported to be 225 nm[50], 228 nm[57] and 236 nm[58].

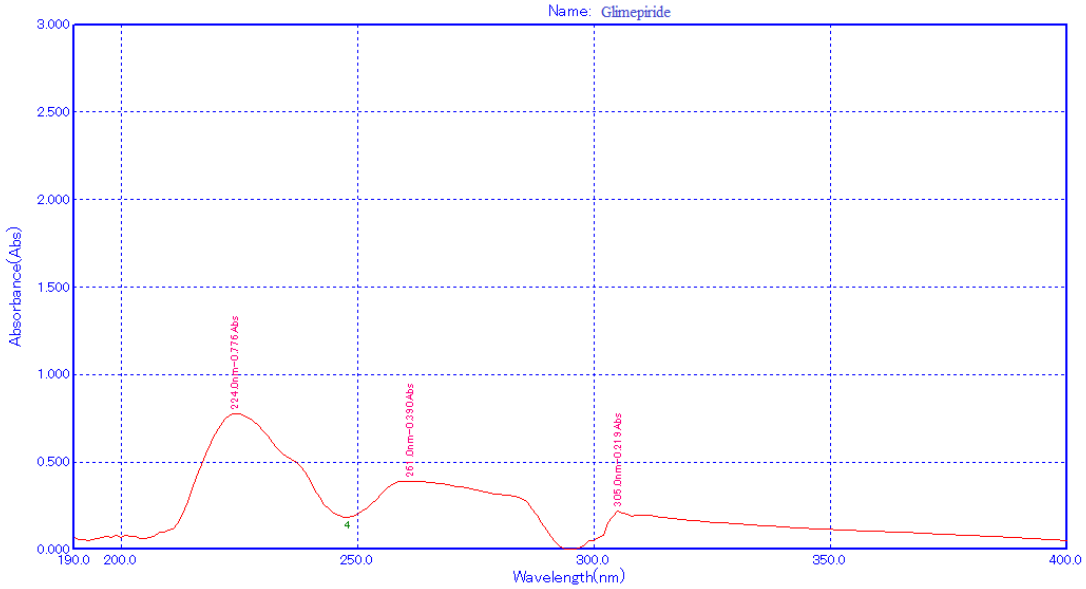

Figure 2.2 UV absorption spectra of Glimepiride

2.1.4 Calibration curve of glimepiride

The calibration curve was constructed using absorbance of 5-25µg/mL solutions of glimepiride at 224 nm (Table 6.3, Figure 6.2). The equation for the calibration curve was generated and was used for calculating the concentration of glimepiride in microspheres and release samples.

Table 2.2 Absorbance of working standards of glimepiride at 224nm

Strength (µg/mL)	Optical Density at 224 nm
5	0.213
10	0.421
15	0.635

20	0.851
25	1.037

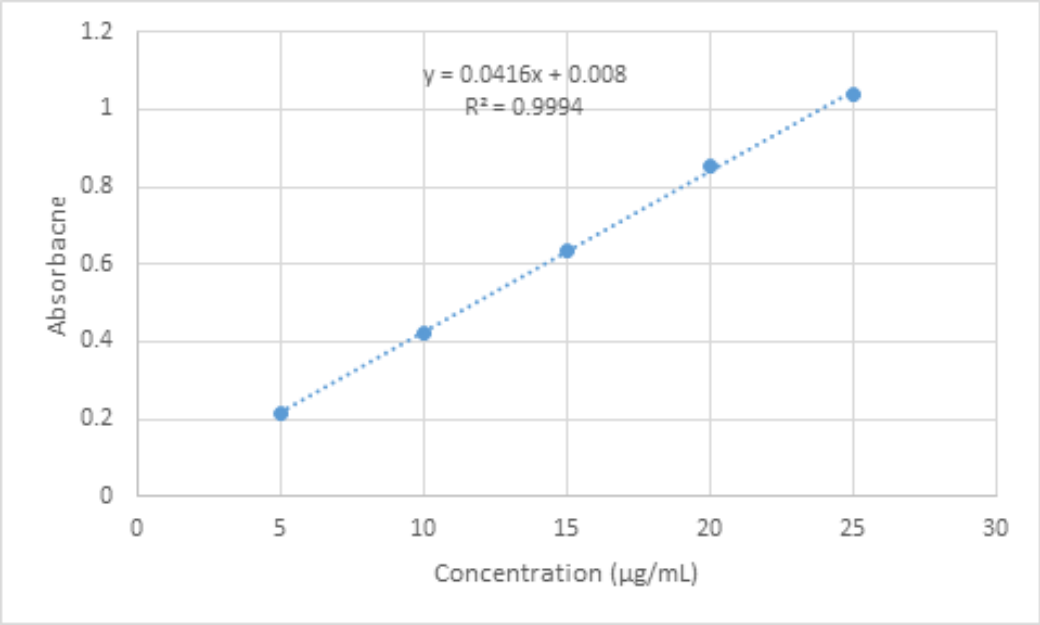

Figure 2.2 Calibration line of glimepiride

As seen from the calibration curve, the regression equation was obtained to be

Absorbance = 0.0415 (concentration) + 0.008

The regression coefficient was obtained to be 0.9994, suggesting the applicability of the equation for accurate analysis of glimepiride.

2.2 Optimization of blend microspheres

Different ratios of gelatin and chitosan were used to study the influence of polymer ratio on particle diameter of the microspheres. The effect of the crosslinking agent (glutaraldehyde) on particles size was also studied.

The particle diameter of the blend microspheres was obtained to be in the assortment of 126.8 µm to 371.3 µm (Table 6.4). The lowest particle diameter (126.8 ± 6.11 µm) was obtained in AF5 containing 50% of gelatin and 50% of chitosan. An increase in the amount of gelatin was linked to decreasing the particle diameter of the microspheres as, the increased gelatin might lead to formation of matrix with higher rigidity.

Table 2.4 Particle diameter of blend microspheres

Formulation	Particle Diameter (µm)	Yield (%)
AF1	371.3 ± 8.29	88.1
AF2	336.4 ± 6.24	83.7
AF3	279.6 ± 8.24	90.6
AF4	235.1 ± 7.33	92.3
AF5	126.8 ± 6.11	93.1
AF6	373.5 ± 9.27	90.8
AF7	372.7 ± 8.13	89.6

The effect of glutaraldehyde was negligible on particle size. As seen from the above table, the particle size obtained using 5% glutaraldehyde was almost equal to that obtained from 2.5 and 7.5% glutaraldehyde. Hence, an intermediate concentration (5% w/w) of glutaraledhyde was used in the optimized formulation. The formulation with the lowest particle size (AF5) was considered the optimized formulation for loading glimepiride.

Glimepiride 20% by weight of the polymer was loaded into the particles during the emulsification phase under stirring.

2.3 Evaluation of Glimepiride loaded blend microsphere

2.3.1 Drug Polymer compatibility study (FTIR)

The FTIR spectra of the physical mixture of glimepiride, gelatin and chitosan displayed all the characteristic peaks of glimepiride, thus indicating that no incompatibility was present between the drug and the polymer (Figure 6.3a, 6.3b).

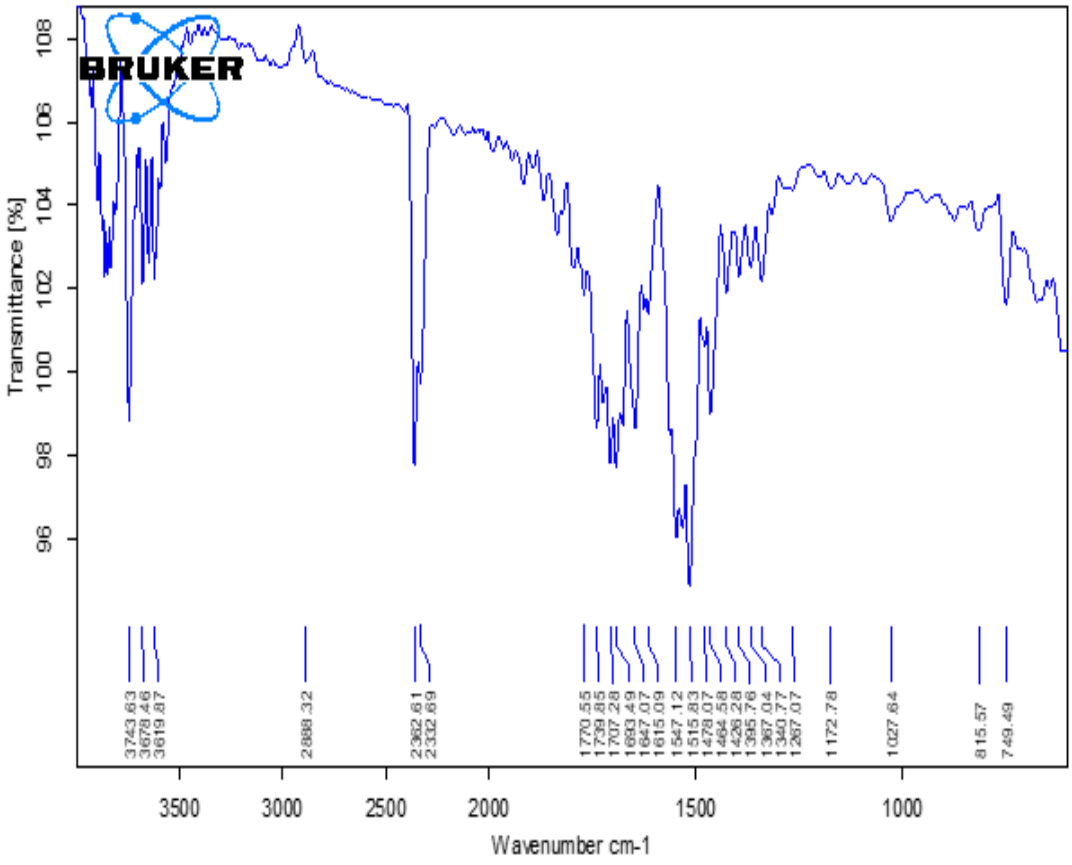

Figure 2.3a FTIR spectrum of Glimepiride

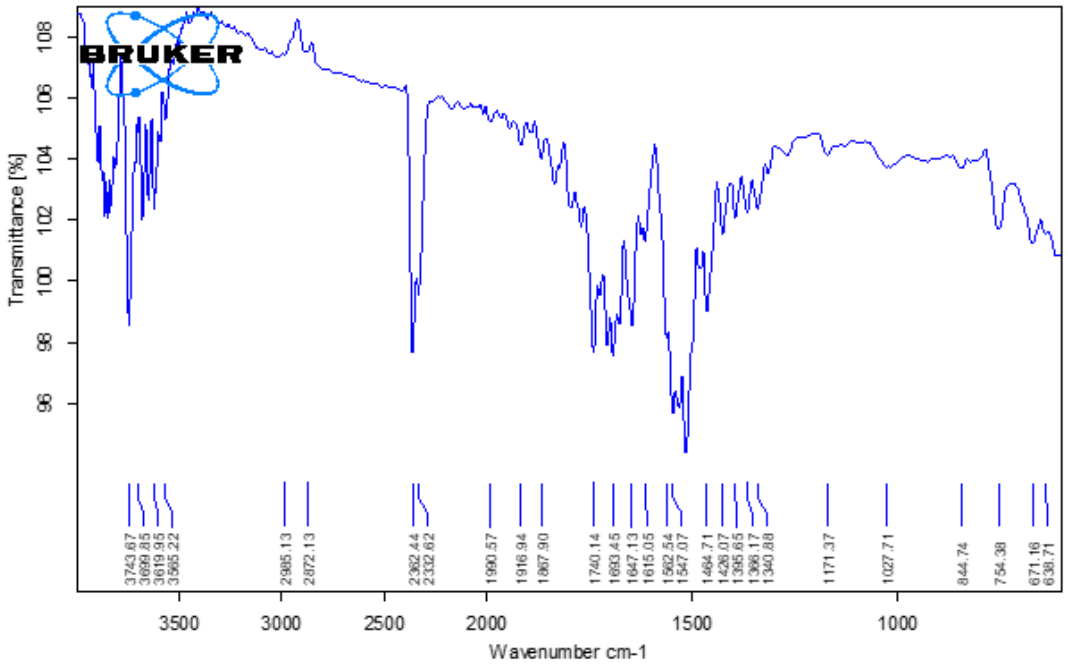

Figure 2.3b FTIR spectrum of physical mixture of chitosan, gelatin and glimepiride

2.3.2 Surface Morphology (SEM)

The SEM image of the drug loaded blend microsphere revealed spherical particles of irregular size with smooth surface (Figure 6.4).

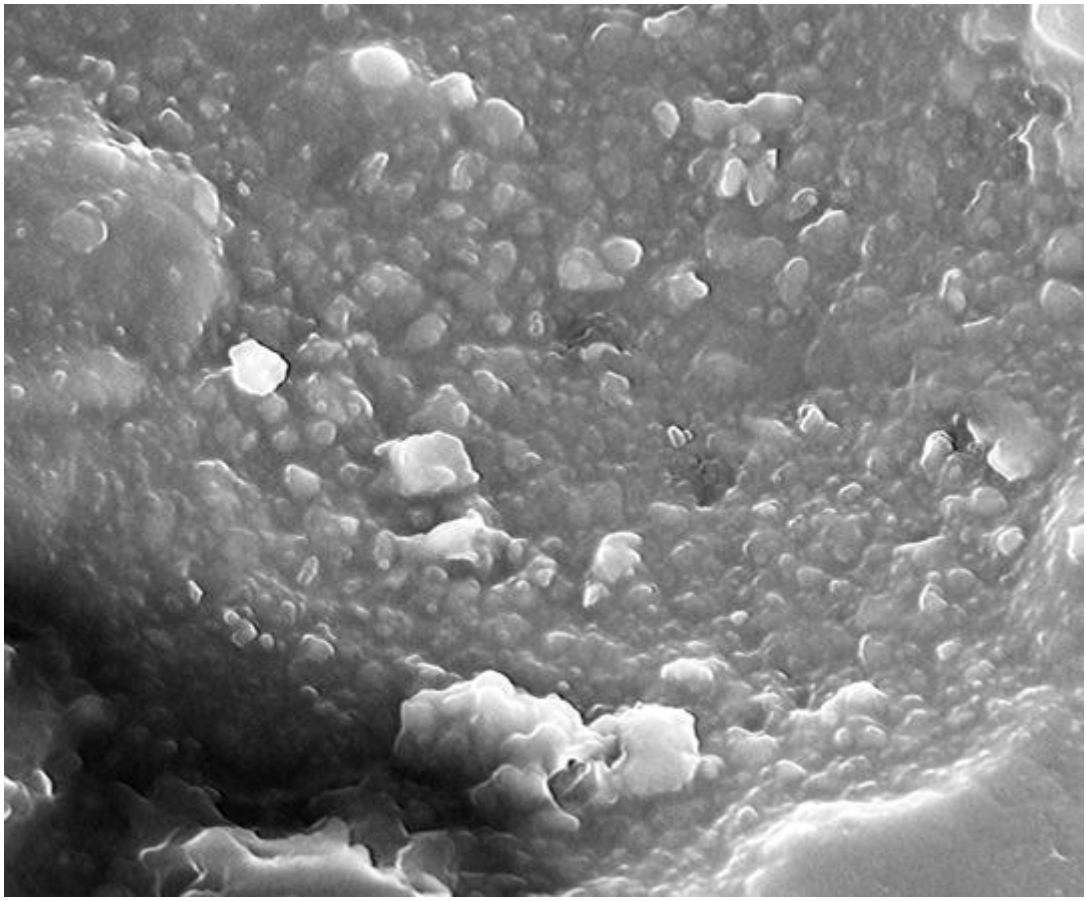

Figure 2.4 SEM of glimepiride loaded blend microsphere

2.3.3 Particle diameter and frequency distribution

The particles size of the microspheres was assessed with the help of calibrated optical micrometer by analyzing 300 particles. The number of particles that appeared in a particular size range was counted and the histogram for frequency distribution was constructed. The histogram (Figure 6.5) revealed that most the particles were in the assortment of 100-150 µm.

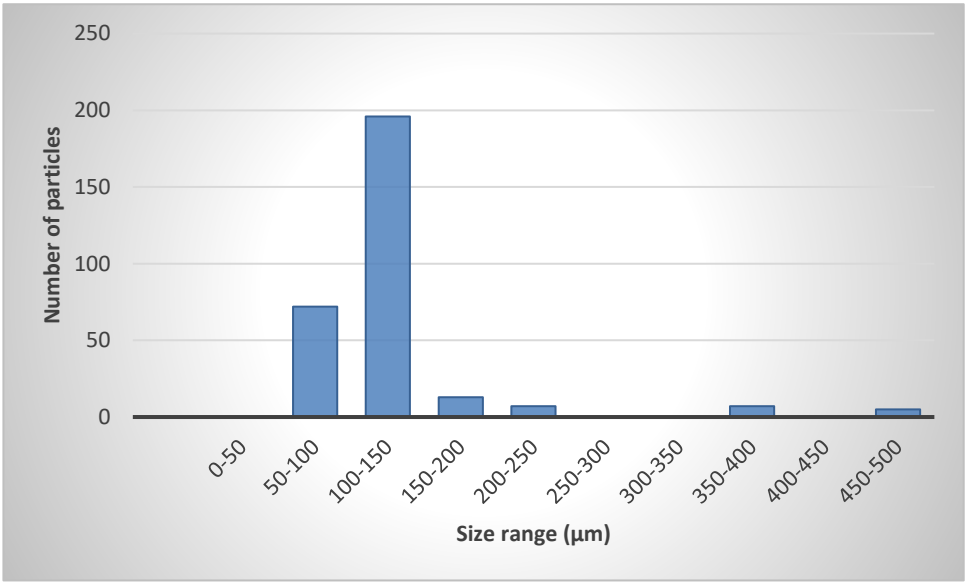

Figure 2.5 Histogram depicting frequency distribution of particles

The average particles diameter of the glimepiride loaded blend microspheres was obtained to be 131.4 ± 9.7 µm with a yield of 91.6% by weight of the drug and polymers used for formulation of the microspheres.

2.3.4 Entrapment efficiency

In order to compute the entrapment efficiency of glimepiride in the blend microspheres, the surface adsorbed drug was first estimated followed by rupturing the microspheres by vortexing and measuring the drug that leaked out of the particles into the solution. While 6.5% of the total drug used of loading was found to adsorbed on the surface of the microspheres, it was found that 82.4 ± 6.8% of glimepiride was found to be entrapped in the particles. The remaining 11% drug was lost in process of formulation of the particles.

2.3.5 *In vitro* drug release

The *in vitro* release study of glimepiride from the blend microspheres exhibited prolonged release. The results of the *in vitro* release studies of the glimepiride loaded blend microsphere revealed that 71.49 ± 0.74 % glimepiride was released from the particles at the end of 12th hour of study (Table 6.5, Figure 6.6).

Table 2.5 Percent glimepiride released from the formulation

Time (h)	% cumulative drug release
0	0
1	5.7 ± 0.57
2	9.46 ± 0.62
3	25.41 ± 0.52
4	29.67 ± 0.61
6	38.27 ± 0.76
8	45.19 ±0.70
10	59.08 ± 0.59
12	71.49 ± 0.74

As found from the result, the sudden release of glimepiride from the blend microspheres after 3rd hour was visible which might be attributed to the leakage of loosely entrapped glimepiride in the core. The almost steady release thereafter indicates that the drug was entrapped within the matrix that was formed by the gelatin and chitosan interlinking.

2.4 Release kinetics of glimepiride from the blend microspheres

The plots of drug release (cumulative percent release, log cumulative percent release, cumulative percent retained) vs time (time, log time, square root of time) were plotted and the release kinetics of the drug from the microspheres was studied.

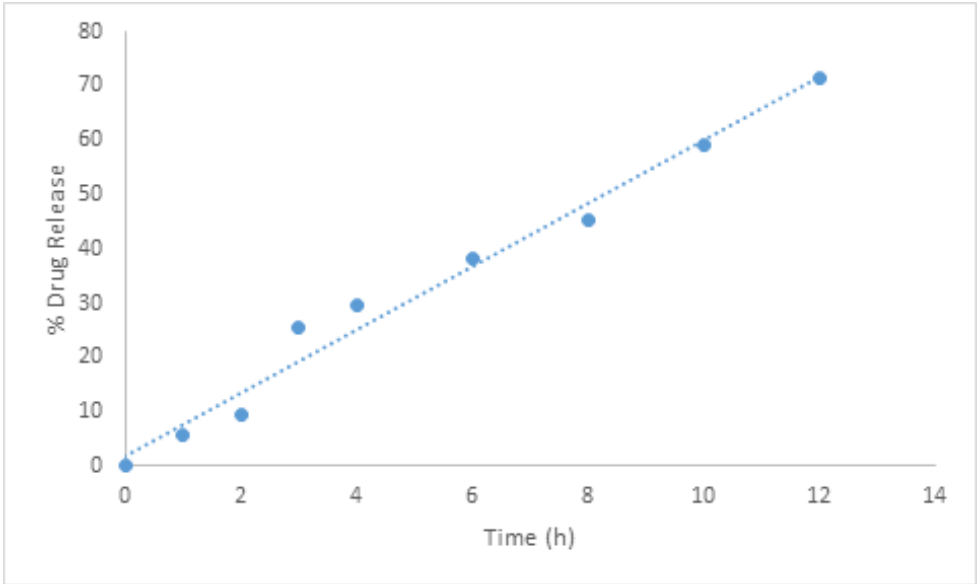

Figure 2.6 Zero order plot of release of glimepiride from blend microspheres

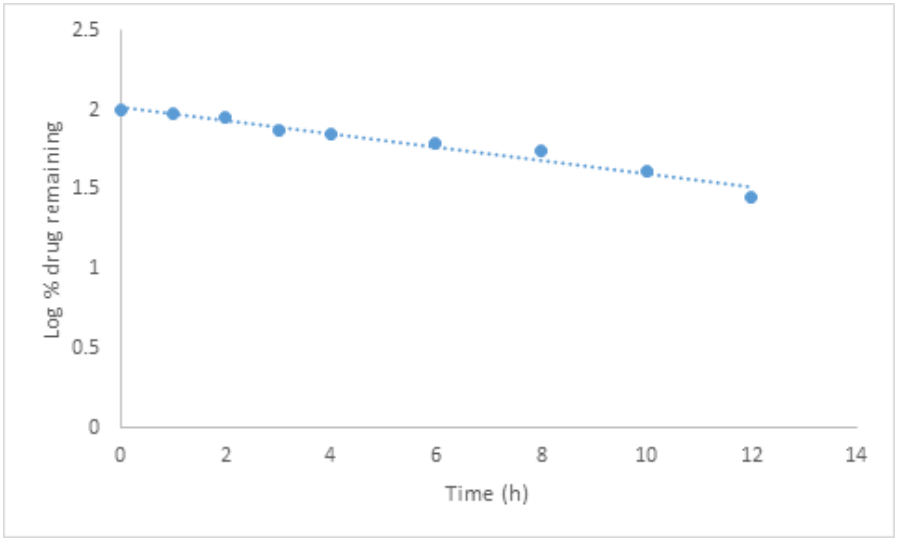

Figure 2.7 First Order plot of release of glimepiride from blend microspheres

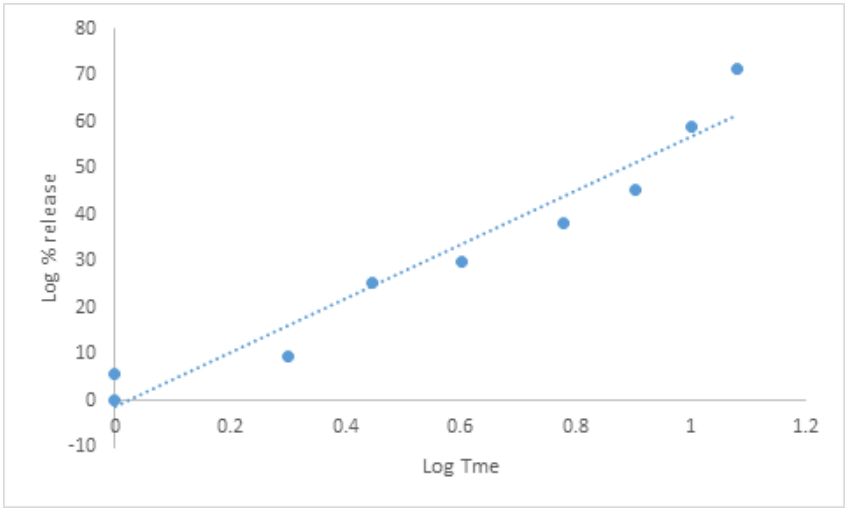

Figure 2.8 Higuchi plot of release of glimperide from blend microspheres

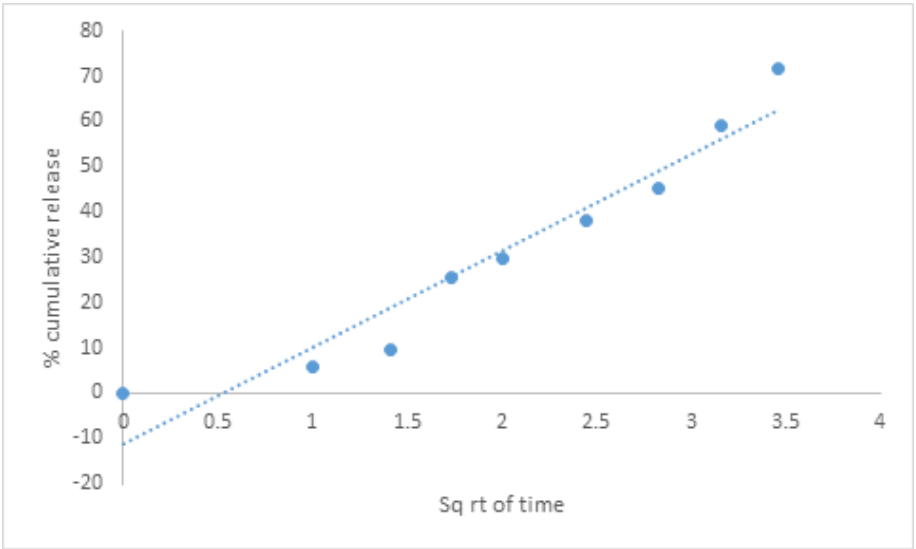

Figure 2.9 Korsemeyer-Peppas plot of release of glimperide from blend microspheres

Table 2.6 Regression coefficient (R^2) of various release models

Zero order	First order	Higuchi	Peppa's
0.9764	0.9601	0.9744	0.9618

The Higuchi equation describes the diffusion controlled release mechanism, and the regression coefficient of determination showed that zero order kinetics was the best fit for the release data.

3. Conflict of Interest

ensure the scientific objectivity of articles appearing in the IJFMR the Journal requires that all authors disclose all potential or perceived conflicts of interest that may exist.

Manuscript title: Name of Author: _Ashif Ali Mansoori_ Signature: *

As the corresponding author, I declare the following informations regarding the specific conflict of interests of authors of our manuscript aforementioned.

Examples of Conflict of Interest: Source of Funding, Paid consultant to Sponsor, Study Investigator Funded Mentioned Product

I accept the responsibility for the completion of this document and attest to its validity on behalf of all co-authors.

Acknowledgement

I wish to acknowledge those persons who were generous in their ways to make me project completely educating program and helped me to bring this report to light. First and foremost, I would like to thank my loving parent's **Ms**. **Julekha Begum,** & **Mr** Anwar Ali Mansoori Without their unconditional support, encouragement and sacrifice, I would never have come so far. I take opportunity to place on record my grateful thanks and sincere graduate to my Professor (Associate Professor & HOD) BHABHA PHARMACY RESEARCH INSTITUTE, BHOPAL (**M**.**P**) whose gave me valuable advice and input for my project work. I am immensely grateful to my **Guide Mr. Rajkumar Dhangar** whose continued and invaluable guidance can never be forgotten by me but for whom this study could not have got present shape. I am thankful to all my batch mates who supported me morally and extended considerable help & support during the course of my study. Who gave me chance of getting industrial exposure during my **M**.**PHARM**A (**Pharmaceutics**) project work. I also want to express my deep sense of gratitude to my advisor I don't have words to thank him for his tremendous effort and noble guidance in completing my project. At last, I would like to thank all dignities for their proper assistance and cooperation which resultedin completion of my thesis report.

4. References

1. Bhabani Shankar N, Uday Kumar N. Lamivudine loaded microspheres for oral use; Design, Development and establishment of In Vivo-In Vitro Correlation. Asian Journal of Pharmaceutical and Clinical Research.2009; 2(1): 55-60.
2. Bijank G, Rabindra D, Soumyadeep G, Manas C, Amitava B. Formulation Development Studies of Bilayer Tablet Glipizide: A novel and Evolutionary Approach in the Treatment of Diabetes. Asian Journal of Pharmaceutical and Clinical Research. 2013; 6(4): 131–137.
3. Srikanth P,Raju N,Wasim Raja S, Brito Raj S. A review on Oral controlled drug delivery. International Journal of Advanced Pharmaceutics.2013; 3(1): 51-58.

4. Brahmankar DM, Jaiswal SB. Biopharmaceutics and Pharmacokinetics - A treatise: 1st edition. Delhi: Vallabh Prakashan; 2000.p 337.
5. Chein YW. Novel Drug Delivery Systems. 2nd edition. New York: Marcel Dekker; 2005. p 139-41.
6. McConville JT. Recent trends in oral drug delivery: Drug Delivery. 2005; 24-26.
7. Gunja C, Prakash B, Saha R.N. Microspheres technology and its applications.(PDF).http://docstoc.com/docs/38166355/review-on-microspheres,Nov 2010
8. Sahil K, Akanksha M, Premjeet S, Bilandi A, Kapoor B.Microsphere:A Review. International Journal of Research in Pharmacy and Chemistry.2011; 1(4): 2231-2781.
9. Alagusundaram M, Madhu Sudana Chetty.C, Umashankari K, Venkata Badarinath A, Lavanya C, Ramkanth S. International Journal of ChemTech Research. 2009; 1(3): 526-534.
10. Bulut E, Assessment of temperature-sensitive properties of ionically crosslinked sodium alginate/hydroxypropyl cellulose blend microspheres: preparation, characterization, and in vitro release of paracetamol. Journal of Biomaterial Science. 2022; Ahead of print. doi: 10.1080/09205063.2022.213507
11. Vasiukhina A, Gad SF, Wellington EN, Wilmes DM, Yeo Y, Solorio L. PLA-PCL microsphere formulation to deter abuse of prescription opioids by smoking. International Journal of Pharmaceutics. 2022; 626: 122151. Doi: 10.1016/j.ijpharm.2022.122151
12. Ghumman SA, Mahmood A, Noreen S, Rana M, Hameed H, Ijaz B, Hasan S, Aslam A, Fayyaz ur Rehman M. Formulation and evaluation of quince seeds mucilage – sodium alginate microspheres for sustained delivery of cefixime and its toxicological studies. Arabian Journal of Chemistry. 2022; 15: 103811. Doi: 10.1016/j.arabjc.2022.103811
13. Mady FM, Ibrahim SRM, Abourehab MAS. Development and Evaluation of Alginate-gum Blend Mucoadhesive Microspheres for Controlled Release of Metformin Hydrochloride. Journal of Advanced Biomedical and Pharmaceutical Sciences. 2021; 4: 111-118
14. Patel AK, Mishra MK, Gupta J, Ghoshal S, Gupta R, Kushwaha K. Guar Gum-Based Floating Microspheres of Repaglinide Using 3^2 Factorial Design: Fabrication, Optimization, Characterization, and In Vivo Buoyancy Behavior in Albino Rats. ASSAY and Drug Development Technologies. 2021; 19(2): 63-74
15. Ozoude CH, Azubuike CP, Ologunagba MO, Tonuewa SS, Igwilo CI. Formulation and development of metformin-loaded microspheres using Khaya senegalensis (Meliaceae) gum as co-polymer. Future Journal of Pharmaceutical Sciences. 2020; 6: 120. Doi: 10.1186/s43094-020-00139-6
16. Okunlola A, Odeniyi MA, Arhewoh MI. Microsphere formulations of ambroxol hydrochloride: influence of Okra (Abelmoschus esculentus) mucilage as a sustained release polymer. Progress in Biomaterials. 2020; 9: 65-80
17. Qushawy M, Nasr A, Swidan S, Mortagi Y. Development and Characterization of Glimepiride Novel Solid Nanodispersion for Improving Its Oral Bioavailability. Scientia Pharmaceutica. 2020; 88: 52. doi:10.3390/scipharm88040052
18. Phromsopha T, Baimark Y. Preparation of Starch/Gelatin Blend Microparticles by a Water-in-Oil Emulsion Method for Controlled Release Drug Delivery. International Journal of Biomaterials. 2014; 829490. Doi: 10.1155/2014/829490
19. Narayana Reddy LC, Reddy RSP, Rao KKSV, Subha MCS, Rao CK. Development of Polymeric Blend Microspheres from Chitosan-Hydroxypropylmethyl Cellulose for Controlled Release of an Anti-Cancer Drug. Journal of the Korean Chemical Society. 2013; 57(4): 439-446

20. Zhang, W.; Chen, X.; Li, P.H.Q.; Zhou, H.; Cha, D. Chitosan and β-cyclodextrin microspheres as pulmonary sustained delivery systems. J. Wuhan Uni. Technol. Mater. Sci. Ed., 2008, 23, 541-546.
21. Angadi, S.C.; Manjeshwar, L.S.; Aminabhavi, T.M. Stearic acid-coated chitosan-based polymer network microspheres: controlled release characteristics. Ind. Eng. Chem. Res., 2011, 50, 4504-4514.
22. Chiming, Y.; David, P.; David, N.; Helen, M.B. PLGA and PHBV Microsphere formulations and Solid-State characterization: Possible implications for local delivery of fusidic acid for the treatment and prevention of orthopaedic infections. Pharm. Res., 2009, 7, 1644-1656.
23. Mundargi, R.C.; Rangaswamy, V.; Aminabhavi, T.M. Spray drying technique to produce controlled release formulations of zidovudine-An anti-HIV drug. J. Appl. Polymer Sci., 2011, 122, 2244-2251.
24. Shelke, N.B.; Rokhade, A.P.; Aminabhavi, T.M. Preparation and evaluation of novel blend microspheres of Poly(lactic-co-glycolic) acid and pluronic F68/127 for controlled release of repaglinide. J. Appl. Polymer Sci., 2010, 116, 366-372.
25. Sridhar, D.; Kumar, G.J.; Ashim, K.M. Effect of polymer blending on the release of ganciclovir from PLGA microspheres. Pharm. Res., 2006, 23, 215-223.
26. Sudha, C.A.; Latha, S.M.; Tejraj, M.A. Interpenetrating polymer network blend microspheres of chitosan and hydroxyethyl cellulose for controlled release of isoniazid. Int. J. Biol. Macromol., 2010, 47, 171-79.
27. Mundargi, R.C.; Shelke, N.B.; Ramesh Babu, V.; Patel, P.; Rangaswamy, V.; and Aminabhavi, T.M. Novel thermoresponsive semi-interpenetrating network microspheres of gellan gum-poly(N-isopropylacrylamide) for controlled release of atenolol. J. Appl. Polymer Sci., 2010, 116, 1832-1841.
28. Biman, B.M.; Jasdeep, K.M.; Kundu, S.C. Silk fibroin/gelatin multilayered films as a model system for controlled drug release. Eur. J. Pharm. Sci., 2009, 37, 160-171.
29. Ramesh, B.V.; Kanth, V.R.; Mukund, J.M.; Aminabhavi, T.M. Novel methyl cellulose-grafted-acrylamide/gelatin microspheres for controlled release of nifedipine. J. Appl. Polym. Sci., 2010, 115, 3542-3549.
30. Ling, Z.; Yu-meng, W.; Yu, Y.; Wen-wu, Z. Polymer blends used to prepare nifedipine loaded hollow microspheres for a floating-type oral drug delivery system: In Vitro evaluation. Arch. Pharm. Res., 2010, 133, 443-50.
31. Vijay Kumar, S.; Shelke, N.B.; Prasannakumar, S.; Sherigara, B.S.; Aminabhavi, T.M. Microspheres of copolymeric N-vinylpyrrolidone and 2-Ethoxyethyl methacrylate for controlled release of nifedipine. Macromol. Res., 2009, 17, 1003-1009.
32. Mundargi, R.C.; Rangaswamy, V.; Aminabhavi, T.M. A Novel Method to Prepare 5-Fluorouracil, An Anti-cancer drug, loaded microspheres from poly(N-vinyl caprolactam-co-acrylamide) and controlled release studies. Designed Monomers Polymers, 2010, 13, 325-336.
33. Mundargi, R.C.; Rangaswamy, V.; Aminabhavi, T.M. Poly (n-vinylcaprolactam-co-methacrylic acid) hydrogel microparticles for oral insulin delivery. J. Microencapsu, 2011, 28, 384-394.
34. Wenlei, J.; Steven, P.S. Stabilization and controlled release of bovine serum albumin encapsulated in poly (D, L-Lactide) and Poly (ethylene glycol) Microsphere blends. Pharm. Res., 2001, 18, 878-85.
35. Preeti, V. K.; Jathi, K. Chitosan-sodium alginate biodegradable interpenetrating network beads for delivery of ofloxacin hydrochloride. Int. J. Pharm. Sci., 2010, 2,77-78.

36. Seong, W.C.; She, H.S.; Young, W.C. Effects of solvent selection and fabrication method on the characteristics of biodegradable poly (lactide-co-glycolide) microspheres containing Ovalbumin. Arch. Pharm. Res., 2000, 23, 385-90.
37. Thomas, L.W.; Dale, T.S.; Tibisay, N.V.; Zhonghui, Y.; Kwon, T.L.; Eun, J.P. Encapsulation of protein nanoparticles into uniformed –sized microspheres formed in a spinning oil film. AAPS Pharm. Sci. Tech., 2005, 6, E605-17.
38. Sullad, A.G.; Manjeshwar, L.S.; Aminabhavi, T.M. Controlled release of theophylline from interpenetrating blend microspheres of poly (vinyl alcohol) and methyl cellulose. J. Appl. Polymer Sci., 2010, 116, 1226-1235.
39. Angadi, S.C.; Manjeshwar, L.S.; Aminabhavi, T.M. Interpenetrating polymer network blend microspheres of chitosan and hydroxyethyl cellulose for controlled release of isoniazid. Int. J. Biol. Macromol., 2010, 47, 171-179.
40. Sullad, A.G.; Manjeshwar, L.S.; Aminabhavi, T.M. Novel pH-sensitive hydrogels prepared from the blends of poly (vinyl alcohol) with Acrylic Acid-graft-Guar Gum Matrixes for Isoniazid Delivery. Ind. Eng. Chem. Res., 2010, 49s, 7323-7329.
41. Sullad, A.G.; Manjeshwar, L.S.; Aminabhavi, T.M. Microspheres of carboxymethyl Guar gum for In Vitro release of abacavir sulfate: preparation and characterization. J. Appl. Polymer Sci., 2011, 122, 452-460.
42. Mundargi, R.C.; Rangaswamy, V.; Aminabhavi, T.M. pH-sensitive oral insulin delivery systems using Eudragit microspheres. Drug Dev. Ind. Pharm., 2011, 37, 977-985.
43. Mundargi, R.C.; Ramesh B. V.; Rangaswamy, V.; Aminabhavi, T.M. Formulation and In Vitro evaluation of transdermal delivery of Zidovudine-An Anti-HIV Drug. J. Appl. Polymer Sci., 2011, 119, 1268-1274.
44. Mohanraj, P.; Jasmina, K. Cellulose based matrix microspheres of prednisolone inclusion complex: preparation and characterization. AAPS Pharm. Sci. Tech., 2011, 12(1), 388-400.
45. https://go.drugbank.com/drugs/DB00222; assessed 01/07/2023
46. https://www.drugbank.ca/drugs/DB14155 assessed on 07/07/2023
47. Rowe RC, Sheskey PJ, Owen SC. Eds. Handbook of Pharmaceutical Excipients. Pharmaceutical Press, 5th ed. 2006; pp 295-298
48. Appendix 13.1 Buffers, In: Indian Pharmacopoeia, 1996, The Indian Pharmacopoeia Commission, Ghaziabad
49. Chaurasia G. A review of pharmaceutical preformulation studies in formulation and development of new drug molecules. Int J Pharm Sci Res. 2016; 7(6): 2313-2320
50. Induri M, Raju BM, Prasad RY, Reddy PK. Development and Validation of A Spectrophotometric Method for Quantification and Dissolution Studies of Glimepiride in Tablets. E-Journal of Chemistry. 2012; 9(2): 993-998
51. Rokhade, A. P.; Agnihotri, S. A.; Patil, S. A.; Mallikarjuna, N. N.; Kulkarni, P. V.; Aminabhavi, T. M. Semi-interpenetrating polymer network microspheres of gelatin and sodium carboxymethyl cellulose for controlled release of ketorolac tromethamine. Carbohydr. Polym. 2006, 65, 243.
52. Pandey GK, Pandey D, Jain D, Joshi A, Dubey BK. Design and Optimization of Lamivudine Floating Microspheres. Journal of Pharmacology and Biomedicine. 2017; 1(1): 15-29.
53. Dipankar O, Gupta M, Dubey BK. Formulation and evaluation of extended release microspheres loaded with labetalol. Journal of Pharmacology and Biomedicine. 2017; 1(1): 15-29.

54. Rekha U, Manjula BP (2011). Formulation and evaluation of microsponges for topical drug delivery of Mometasone furoate. Internat J Pharmacy Pharm Sci. 3(4):133-137.
55. Shaikh KS, Chellampillai B, Pawar AP (2010). Studies on nonionic surfactant bilayer vesicles of ciclopirox olamine. Drug Dev Ind Pharmacy. 36(8): 946-953.
56. https://cdn.caymanchem.com/cdn/insert/12090.pdf
57. Patel C, Suthar D, Patel H, Movaliya V, Parejiya P. Performulation study of Glimepiride: An insight for formulation and development of parenteral formulation. Journal of Pharmaceutical Research International. 2022; 34(15B): 38-49.
58. Reichel RC. Formulation and evaluation of glimepiride as gastro retentive dosage form. M.Pharm Thesis, 2009.

Licensed under Creative Commons Attribution-ShareAlike 4.0 International License