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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF METFORMIN HYDROCHLORIDE MICROSPHERES

***Dr. Sandeepthi, N. and Jhancy Laxmi Bai, N.**

Department of Pharmaceutics, Omega College of Pharmacy, Edulabad, Ghatkesar, Medchal, Telangana, India

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ABSTRACT

Mono or multi nuclear materials embedded in spherical coating matrix are called microspheres. Microspheres are solid, approximately spherical particles ranging in size from 1µm to 1000µm .These are made of polymeric, waxy or other protective materials that are biodegradable synthetic polymers and modified natural products such as starches, gums, proteins fats, and waxes.Microspheres are small and have large surface to volume ratios. At the lower end of their size range they have colloidal properties. The interfacial properties of microspheres are extremely important, often dictating their activity. In fact principle of microsphere manufacture depends on the creation of an interfacial area, involving a polymeric materials that will form an interfacial boundary and a method of cross-linking to impart permanency. The method of manufacturing described later are by no means comprehensive and the reader should bear in mind that if the aforementioned criteria are adhered to, the only limitation to the manufacture of microspheres is the researchers imagination. Preparation of microspheresneed mainly two ingredients. They are Core material – drug, Coating material – polymer.

INTRODUCTION

Microencapsulation is one of the newly developed technique. Microencapsulation is a process of incorporating drugs into small size multi particulate units. As a process it is a means a applying relatively thin coatings to small particles of solids or droplets of liquids. Microencapsulation developed for use in medicine consists of solid or liquid core material containing one or more drugs enclosed in coating material. The core may also be referred as nucleus and the coating as wall or sheet. Depending upon manufacturing process various types of products are obtained in microencapsulation.

These products are

- **Microcapsules** – mono or multinuclear material enclosed by a coat or membrane are called as microcapsules.
- **Microspheres** – mono or multinuclear material embedded in spherical coating matrix are called microspheres.

Since 1960, the technique of microencapsulation has been used in pharmaceutical industry. The advantages of microencapsulation are:

- Masking odour and taste of drugs.
- Conversion of oil and other liquids into solids for the ease of handling.
- Protecting of drugs from environmental conditions like moisture, heat and light.
- Separation of incompatible materials.
- Volatilization of encapsulated material can be delayed or prevented.
- Improvement of flow properties of the powder.
- Safe handling of substances.
- Sustained release or controlled release or targeted medication can be achieved.

Apart from all the above mentioned advantages the phenomenon of microencapsulation has few limitations. Process conditions like change in temperature, pH, solvent addition , evaporation or agitation may effect the stability of core particles to be encapsulated and reproducibility is less and both the end products, Microcapsules and microspheres, bare their own advantages and disadvantages. The concept of microspheres dates to the 1930s and to the work of Bugerbergdejong and coworkers on the entrapment of the substances with in coacervates by national cash register company for the manufacture of carbonless copying paper. The usage of microsphere technology by pharmaceutical industry has been since 1960s. This process of microencapsulation has been used medically for the encapsulation of live cells and vaccines.

Corresponding author: **Dr. Sandeepthi, N.,**
Department of Pharmaceutics, Omega College of Pharmacy, Edulabad, Ghatkesar, Medchal, Telangana, India.

Biocompatibility of biomolecules like proteins, peptides, hormones and artificial cells can be improved by encapsulating.

METHODS

Preparation of Metformin Hydrochloride Microspheres

Ethyl cellulose microspheres containing Metformin HCl were prepared by solvent evaporation method. Ethylcellulose was dissolved in acetone to form a homogeneous polymer solution. Metformin HCl was added to polymer solution and dispersed thoroughly. The resulting mixture was then added in a thin stream to the liquid paraffin in a 250ml beaker under stirring at 1000rpm to disperse the added mixture as fine droplets. System was stirred to evaporate the solvent at room temperature for 2hrs to form ethyl cellulose microspheres of Metformin HCl.Prepared microspheres were collected by filtration and washed with cyclohexane to remove adhering liquid paraffin7. Microspheres were dried over night at 40ºC and stored in a well closed container. Similarly, Plasticized Ethyl Cellulose Microspheres were prepared by using N-dibutyl phthalate as plasticizer by adding it to the homogeneous polymer solution by adopting the above method.

METHOD

Solvent evaporation

It is most extensively used method of microencapsulation. A buffered or plain aqueous solution of the drug (may contain a viscosity building or stabilizing agents)is added to an organic phase consisting of the polymer solution in solvents like dichloromethane(or ethyl acetate or chloroform)with vigorous stirring to form the primary water in oil emulsion. This emulsion is then added to a large volume of water containing an emulsifier like PVA or PVP to form the multiple emulsion(w/o/w). The double emulsion ,so formed is then subjected to stirring until most of the organic solvent evaporates, leaving solid microspheres. The microspheres can then be washed, centrifuged and lyophilized to obtain the free flowing and dried microspheres.

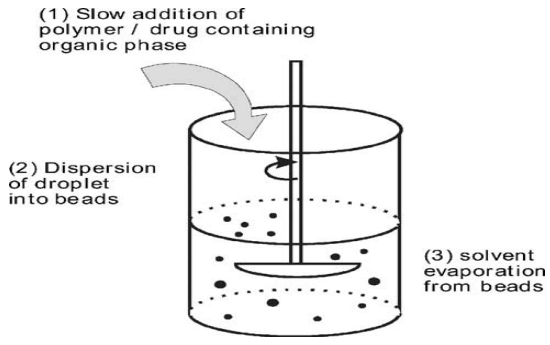

Fig-1: Depiction of sphere formation by solvent evaporation. A solvent-polymer droplet disperses inside the continuous phase forming solvent-polymer spheres; the sphere hardens as the organic solvent evaporates

Hot melt microencapsulation

This method is used to prepare microspheres of polyanhydride copolymer of poly[bis(p-carboxyphenoxy)propane anhydride] with sebacic acid.

In this method the polymer is first melted and then mixed with solid particles of the drug that have been sieved to less than 50µm. The mixture is suspended in a non –miscible solvent (like silicon oil) continuously stirred, and heated to 5ºc above the melting point of the polymer .Once the emulsion is stabilized , it is cooled until the polymer particles solidify. The resulting microspheres are washed by decantation with petroleum ether. The primary objective for developing this method is to develop a microencapsulation process suitable for the water labile polymers e.gpolyanhydrides. Microspheres with diameter of 1-1000µm can be obtained and the size distribution can be easily controlled by altering the stirring rate. The only disadvantage of this method is the moderate temperature to which the drug is exposed.

Solvent removal

It is a non- aqueous method of microencapsulation, particularly suitable for water labile polymers such as the polyanhydrides. In this method, drug is dispersed or dissolved in a solution of the selected polymer in a volatile organic solvent like methylene chloride .this mixture is then suspended in silicon oil containing span 85 and methylene chloride. After pouring the polymer solution into silicon oil, petroleum ether is added and stirred until solvent is extracted into the oil solution. The resulting microspheres can then dried in vacuum.

Spray drying

In this process, the drug may be dissolved or dispersed in the polymer solution and spray dried. The quality of spray-dried microspheres can be improved by the addition of plasticizers, e.g citric acid , which promote polymer coalescence on the drug particles and hence promote the formation of spherical and smooth surfaced microspheres. The size of microspheres can controlled by the rate of spraying, the feed rate of polymer drug solution, nozzle size, and drying temperature. This method of microencapsulation is particularly less dependent on the solubility characteristics of the drug and polymer and is simple, reproducible and easy to scale up.

Phase inversion microencapsulation

The process involve addition of drug to a dilute solution of the polymer (usually 1-5%, w/v in methylene chloride). The mixture is poured into an unstirred bath of a strong non-solvent (petroleum ether) in a solvent to non-solvent ratio of 1:100, resulting in the spontaneous production of microspheres through phase inversion. The microspheres in the size range of 0.5-5.0 µm can then be filtered, washed with petroleum ether and dried with air. This simple and fast process of microencapsulation involves relatively little loss of polymer and drug.

Freeze drying

This technique involves the freezing of the emulsion, the relative freezing point of continuous and dispersed phase are important. The continuous phase solvent is usually organic and is removed by sublimation at low temperature and pressure. Finally the dispersed phase solvent of the droplets is removed by sublimation, leaving polymer drug particles.

Chemical and thermal cross linking

Microspheres made from natural polymers are prepared by a cross-linking process, polymer include gelatin, albumin, starch and dextran.

A water –oil emulsion is prepared where the water phase is a solution of the polymer that contains the drug to be incorporated. The oil phase is a suitable vegetable oil or oil-organic solvent mixture containing an oil-soluble emulsifier. Once the desired water-oil emulsion is formed, the water soluble polymer is solidified by some kind of cross- linking process. This may involve thermal treatment or the addition of a chemical cross- linking agent such as glutaraldehyde to form a stable chemical cross-link as in albumin. If chemical or heat cross-linking is used, the amount of chemical and the period intensity of heating are critical in preparation.

Precipitation

Precipitation is a variation on the evaporation method. The emulsion consists of polar droplets dispersed in a non-polar medium. Solvent may be removed from the droplets by the use of a cosolvent. The resulting increase in the polymer drug concentration causes precipitation forming a suspension of microspheres.

Emulsion method

O/w emulsion is produced by agitation of two immiscible liquids. The drug substance is either dispersed or in solution in polymer/solvent system or is captured in the dispersed phase of the emulsion. Agitation of the system is continued until the solvent partition into the aqueous phase and is removed by evaporation.

Loading Of Drug

The active components are loaded over the microspheres principally using two ways.

- During the preparation of microspheres .
- After the formulation of microspheres by incubating them with the drug or protein.

Drug can be loaded by means of

- Physical entrapment.
- Chemical linkage.
- Surface adsorption.

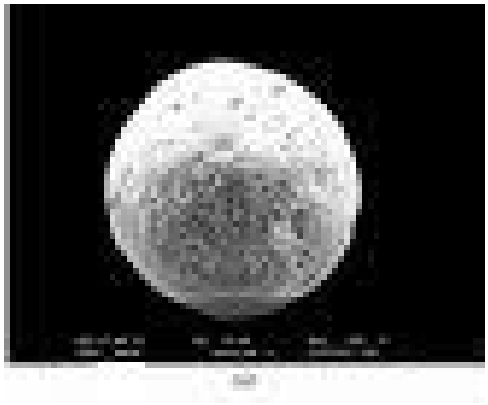

Fig. 2. Drug loaded microspheres

Design of controlled and sustainedrelease

Products

Principle behind Sustained/Control drug release

Dissolution and diffusion controlled systems have classically been of primary importance in oral delivery of medication because of their relative ease of production and cost compared with other methods of sustained or controlled delivery. Most of these systems are solids, although a few liquids and suspensions have been recently introduced.

The classifications of such systems are as follows

Diffusion controlled systems

Diffusion systems are characterized by the release rate being dependent on its diffusion through an inert membrane barrier. Usually this barrier is an insoluble polymer. In general two types of sub classes of diffusion systems are recognized they are:

- Reservoir devices.
- Matrix devices.

Reservoir devices

Reservoir devices are characterized by a core drug reservoir surrounded by a polymeric membrane. The nature of membrane determines the rate of release of drug from the system.

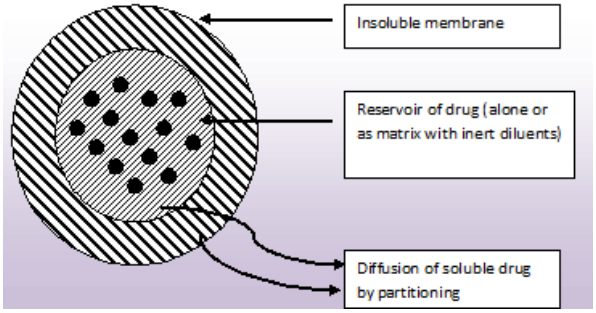

Fig. 3. Schematic representation drug release of diffusion across the insoluble membrane of Reservoir device.

The process of diffusion is generally described by Fick's equation:

$J = -D\, dc/dx$

Where,

J -- Flux (amount/area-time).

D -- Diffusion co-efficient of drug in the membrane (area/time).

dc/dx -- rate of exchange in concentration C, with respect to a distance

X in the membrane.

Matrix devices

It contains of drug dispersed homogeneously throughout a polymer matrix. In this model, drug in the outside layer exposed to bath solution is dissolved first and then diffuses out of the matrix. The following equation describes the rate of release of drug dispersed in an inert matrix system have been derived by Higuchi:

$Dm/dh = Cod_h – Cs/2$

Where,

Dm = Change in the amount of drug released per unit area.

d_h= Change in the thickness of zero of matrix that have been depleted of drug.

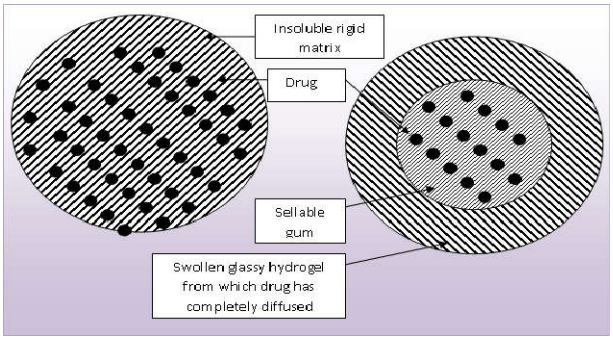

Fig. 4. Schematic representation diffusion controlled devices of rigid matrix & swellable matrix

Co = total amount of drug in unit volume of matrix.
Cs = saturated concentration of drug within the matrix.

The reason for the attenuation of drug release rate in Higuchi profile that when a matrix tablet is placed in the dissolution medium, the initial drug release occurs from the tablets superficial layers and consequently, the release rate in is relatively fast. As time passes, the external layers of the tablet become depleted of the drug and water molecules must travel through long, tortuous channels to reach the drug remaining in the deeper layers of the tablet. Similarly, the drug solution that is formed within the tablet must diffuse through long capillaries to reach the external dissolution medium. The primary reason for the continuously decreasing rate of drug release is the increasing distance that must be traversed by water and drug molecules into and out of the tablet respectively. Therefore any mechanism that lessens the time dependent increase in the diffusion path length would reduce the attenuation of dissolution rate.

Diffusion rate modifications

- Thickness of the separating layer.
- Porosity.
- Partition coefficient.
- Modification of the diffusion co-efficient.
  - Modification of efficient molecular size.
  - Modification of viscosity.
- Modification of concentration.

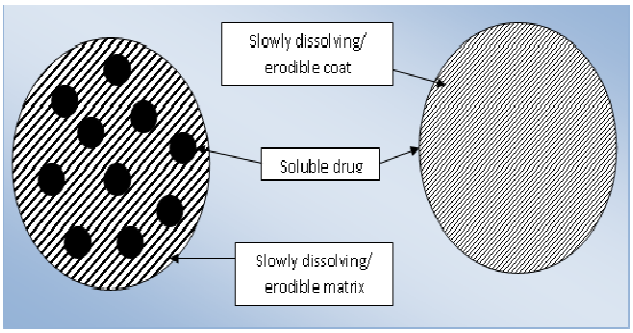

Fig. 5. Schematic representation of dissolution controlled release system

Dissolution – controlled systems

Drug with a slow dissolution rate will demonstrate sustaining properties, since the release of the drug will be limited by rate of dissolution.

These being the case, sustain release preparations of drugs could be made by decreasing their dissolution rate. This includes preparing appropriate salts or derivatives, coating the drug with a slowly dissolving material, or incorporating it into a tablet with a slowly dissolving material, or incorporating it into a tablet with a slowly dissolving carrier. This system is the combination of both diffusion and dissolution of matrix material and the drug. Drug not only can diffuse out of the dosage form but the matrix itself undergoes a dissolution process.

Osmotically controlled systems

This device is fabricated as tablet that contains water soluble osmotically active drug, of that was blended with osmotically active diluents by coating the tablet with a cellulose triacetate barrier which functions as semi permeable membrane. A laser is used to form a precision orifice in the barrier, through which the drug is released due to development of osmotic pressure difference across the membrane, when this was kept in water.

Ion exchange systems

These are salts of cationic or anionic exchange resins or insoluble complexes, in which drug release results from exchange of bound drug ions that are normally present in GI fluids.

Diabetes mellitus

Diabetes mellitus is a group of metabolic diseases characterized by high blood sugar (glucose) levels that result from defects in insulin secretion, or its action, or both. Diabetes mellitus, commonly referred to as diabetes was first identified as a disease associated with "sweet urine," and excessive muscle loss in the ancient world. Elevated levels of blood glucose (hyperglycemia) lead to spillage of glucose into the urine, hence the term sweet urine.

Normally, blood glucose levels are tightly controlled by insulin, a hormone produced by the pancreas. Insulin lowers the blood glucose level. When the blood glucose elevates (for example, after eating food), insulin is released from the pancreas to normalize the glucose level. In patients with diabetes, the absence or insufficient production of insulin causes hyperglycemia. Diabetes is a chronic medical condition, meaning that although it can be controlled, it lasts a lifetime.

METHODS

Preformulation Studies

Preformulation was the first step in the rational development of dosage forms of a drug substance. It can be defined as" an investigation of physical and chemical properties of a drug substance alone and when combined with excipients".

Organoleptic properties

The Organoleptic character of the drug like color, odor and appearance play an important role in the identification of the sample and hence they should be recorded in a descriptive terminology. The results were given in results and discussion section.

Solubility Studies

It is important to know about solubility characteristics of a drug in lipophilic systems, since they must possess some limited solubility in lipophilic systems as the drug is lipid soluble, to elicit a therapeutic response. Solubility was carried out in methanol, ethanol, dichloromethane, water and other solvents. The results were given in results and discussion section.

Melting point

Melting point of metformin hydrochloride drug was determined by melting point apparatus. The results were given in results and discussion section.

Method of Preparation

Solvent evaporation method[115]

Metformin hydrochloride microspheres were prepared by solvent evaporation technique. For this metformin and polymer were dissolved in mixture of dichloromethane and acetonitrile solution. Both drug and polymer solution were mixed well to form a uniform solution. Then add required amount of water to it and stir using homogenizer at 500rpm speed for 2minutes till an emulsion is formed. The obtained emulsion was added (1ml) in intervals of 10min each to the liquid paraffin and span-80 mixture, before adding of drug liquid paraffin and span-80 were stirred for 10min under constant stirring at 500 rpm. The constant stirring continued using homogenizer at 500rpm for 2hr . The microspheres formed were collected by whatmann filter paper and washed with distilled petroleum ether and dried at room temperature for one day to collect microspheres.

Evaluation of Microspheres

Preparation of linearity plot of metformin hydrochloride
Determination of percentage yield[115]

The dried microspheres were weighed and percentage yield of the prepared microspheres was calculated by using the following formula

$$\text{Percentage yield} = \frac{\text{Practical yield (mg)} \times 100}{\text{Theoretical yield}}$$

Determination of Drug Loading

$$\text{Drug loading} = \frac{\text{weight of drug in microspheres} \times 100}{\text{microspheres sample weight}}$$

Determination of mean particle size of microspheres [3]

Particle size distribution of microspheres was carried out by optical microscopy. A minute quantity of dried microspheres was suspended in glycerin and the particle size of 100 microspheres was determined in each batch and the mean particle size was calculated.

Scanning electron microscopy (SEM)

For the external morphology studies, air dried particles were visualized using scanning electron microscopy (FEI-Quanta 200F) operating at 15 kv. The samples were mounted on a metal slab with double adhesive tape and coated with platinum under vacuum[4].

Fourier transform infra red spectroscopy (FTIR)

The fourier transform infra red analysis was conducted for the structure characterization. FTIR spectra of the formulated microspheres and drug were recorded. Microspheres were taken in a KBr pellet using Bomem FTIR MB-II instrument. Approximately 5mg samples were mixed with 50mg of spectroscopic grade KBr, samples were scanned in the IR range from 500-3500cm^{-1}, with a resolution of $4cm^{-}$

In vitro release studies

The in-vitro drug release studies were conducted in p^H 6.8 buffer for 8hrs using USP type –II dissolution apparatus under sink conditions. Accurately weighed samples of the microspheres were filled in a capsule and added to the dissolution medium kept at 37± 0.5^0c .At present time intervals aliquots were withdrawn and replaced by an equal volume of dissolution medium to maintain constant volume. After suitable dilution samples were analysed spectrophotometrically at 242nm.

STUDY OF RELEASE KINETICS

In vitro dissolution has been recognized as an important release element in drug development. Under certain conditions it can be used as a surrogate for the assessment of bioequivalence. The quantitative interpretation of the values obtained in the dissolution assay is facilitated the usage of a generic equation that mathematically translates the dissolution curve in function of some parameters related with the pharmaceutical dosage forms. In some cases, that equation can be deduced by a theoretical analysis of the process, as for example in zero order kinetics. In most cases, with tablets, capsules, coated forms or prolonged release forms that theoretical fundamental does not exist and sometimes a more adequate empirical equation is used. To compare dissolution profiles between two drug products model dependent (curve fitting), statistic analysis and model independent methods can be used. The various release kinetic equations in which the experimental data can be fitted and drug release rate can be predicted as a function of some variable (e.g. time) are mentioned below. The suitability of equation is judged on the basis of best fit to the equation using statistical indicators like R^2 value.

Zero order kinetics

Assumption

Drug dissolution is from a pharmaceutical dosage forms that does not disaggregate and releases the drug slowly (assuming that area does not change and no equilibrium conditions are obtained). The equation describing the kinetics is depicted in equation 1.

$$Q_t = Q_o + K_o t \qquad 1$$

Where,

Q_t is the initial amount of drug dissolved at time t,
Q_o is the initial amount of drug in the solution, most of the times it is equal to zero,

K_o is the zero order release rate constant.
Dosage forms following this profile, release same amount of drug per unit time, and it is the ideal method of release for a sustained release product

First order kinetics

The application of this model to drug dissolution studies was first proposed by Gibaldi and Feldman in 196738.

Equation:

$$Q_t = Q_0 e^{-K_1 t} \quad \text{or} \quad \ln\left(\frac{Q_t}{Q_0}\right) = K_1 t \quad \text{or} \quad \ln q_t = \ln Q_0 K_1 t$$

or in Logarithms

$$\log Q_t = \log Q_0 + \frac{K_1 t}{2.303} \qquad 2$$

Where,

Q_t is the initial amount of drug dissolved at time t,
Qo is the initial amount of drug in the solution,
K_1 is the first order release rate constant
In this way a graphic of the decimal log of the released amount of drug vs. time will be linear.

The pharmaceutical dosage forms following this dissolution profile, such as those containing water soluble drugs in the porous matrices would release the drug in a way that is proportional to the amount of drug remaining in its interior.

Higuchi model

This model was first proposed by Higuchi, 1961 to describe dissolution of drug in suspension from ointment bases, but is widely applicable to other types of dosage forms 39, 40.

The Equation describing release:

$$f_t = Q = \sqrt{D(2C - C_s)C_s t} \qquad 3$$

Where,

Q is the amount of drug released at time t per unit area,
C is the initial concentration,
Cs is the drug solubility in matrix media,
D is the diffusivity of the drug molecule (Diffusion Constant) in the matrix substance.

The above equation is based on the assumptions that the initial drug concentration in the system is much higher than the solubility of drug. This assumption is very important because it provides the basis for the justification for the applied pseudo steady state approach. The suspended drug is in a fine state such that the particles are much smaller in diameter than the thickness of the system. Swelling or dissolution of the polymer carrier is negligible. The diffusivity of the drug is constant and perfect sink conditions are maintained.

Simplified Higuchi model

$$f_t = K_H t^{1/2} \qquad 4$$

Where,

KH is the Higuchi dissolution constant, It describes drug release as a function of square root of time that is dependent on diffusion process based on Fick's Law.

Hixson Crowell model

Hixson and Crowell model recognizing that the particle regular area is proportional to the cubic root of its volume [41]
Equation:

$$W_0^{1/3} - W_t^{1/3} = K_s t \qquad 5$$

Where,

W_0 is the initial amount of drug in the pharmaceutical dosage form, W_t is the remaining amount of drug in dosage form at time t,

K_s is the constant relating surface volume ratio.

This expression applies to pharmaceutical dosage form such as tablets, where the dissolution occurs in planes that are parallel to the drug surface if the tablet dimensions diminish proportionally, in such a manner that the initial geometrical form keeps constant all the time.

Simplified equation:

$$(1 - f_t)^{1/3} = 1 - K_\beta t \qquad \textit{eq-6}$$

Where,

ft = 1-(Wt / W0), represents drug dissolved fraction at time t,
Kβ is the release constant. A graph of the cubic root of the unreleased fraction of drug versus time will be linear if the equilibrium conditions are not reached and if the geometrical shape of the pharmaceutical dosage form diminishes proportionally over time. It is assumed that the release rate is limited by the drug particles dissolution rate and not by the diffusion that might occur through the polymeric matrix.

Korsmeyer- Peppas model

For prediction of mechanism of drug release through polymeric system Korsmeyer and Peppas, in 1983 developed a mathematical equation, relating exponentially the drug released to the elapsed time. It is a simple semi empirical equation also called as *Power law.*

$M_t/M_\infty = Kt^n$ *eq-7*

Where,

M and M_∞ are the absolute cumulative amount of drug released at time t and infinite time, k is a constant incorporating structural and geometric characteristics of the device, n is the drug release exponent, indicative of the mechanism of drug release. To characterize the mechanism for both solvent penetration and drug release n can be used as abstracted. A plot between log of Mt \ Mα against log of time will be linear if the release obeys Peppas & Korsmeyer equation and the slope of this plot represents n value. Interpretation of diffusion exponent and solute release mechanism for cylindrical shape release mechanisms from polymeric film. The values of n representing drug release mechanism for different geometry are shown in Table no 1.

Table 1. Exponent n of Power law and drug release mechanism from polymeric controlled drug delivery system of different geometry

Exponent, n			Drug Release Mechanism
Thin Film	Cylinder	Sphere	
0.5	0.45	0.43	Fickian Diffusion
0.5<n<1.0	0.45<n<0.89	0.43<n<0.85	Anomalous Transport
1.0	0.89	0.85	Case II transport

From the Table 3 it is clear that when the exponent n takes a value of 1.0, the drug release rate is independent of time. This case corresponds to zero order release kinetics For slabs, the mechanism that creates the zero-order release is known to polymer scientists as case-II transport. Here the relaxation process of the macromolecules occurring upon water imbibition into the system is the rate controlling step. The value of n= 0.5 indicates drug release is Fickian in nature. Thus, Equation has two distinct physical meanings in the two special cases of n=0.5 (indicating diffusion-controlled drug release) and n=1 (indicating swelling-controlled drug release). Values of *n* between 0.5 and 1.0 can be regarded as an indicator for the superposition of both phenomena (anomalous transport). It has to be kept in mind that the two extreme values for the exponent *n*, 0.5 and 1.0, are only valid for slab geometry. Power Law is more comprehensive in describing the drug release as compared to Higuchi. The release profiles of different batches of microspheres were fitted for different models such as Zero order, First order, Higuchi and Korsmeyer- peppas plots.

RESULTS AND DISCUSSION

Preformulation Studies

In Preformulation studies drug characteristics was performed and results were complies with pharmacopoeial values.

Drug and Excipients Compatibility Studies

Fourier Transform Infrared Spectroscopy

FTIR spectroscopy was used to ensure that no chemical interactions between the drugs and polymer had occurred. The wave numbers of final formulation and individual ingredients were compared, Hence it was concluded that no chemical interactions were found between drug and polymer.

Evaluation of Microspheres

Linearity plot of metformin hydrochloride in dichloromethane

The solutions of metformin hydrochloride were prepared and the absorbance of resulting solutions was measured in UV spectrophotometer at nm. The absorbance are noted and given in table3. The standard graph between concentration Vs absorbance was given in figure no-9.

Percentage yield, entrapment efficiency, drug loading of microspheres

Mean Particle Size

Mean particle size was determined by optical microscopy and the average particle size was calculated .The results were shown in figure

Scanning Electron Microscopy

The microspheres prepared by solvent evaporation method showed a good sphericity, with smooth surface and the particles were distributed uniformly without any lumps.

In-vitro release studies

The in-vitro release profile of metformin hydrochloride microspheres were conducted in ph buffer for hours.

Table 2. Metformin hydrochloride preformulation studies

S.NO	PARAMETERS	REPORT
1	Physical appearance	white fine crystalline power .
2	Solubility	Soluble in water, 95% alcohol. Practicallyinsoluble in ether, chloroform.
3	Melting point	218-220˚C; 232˚C

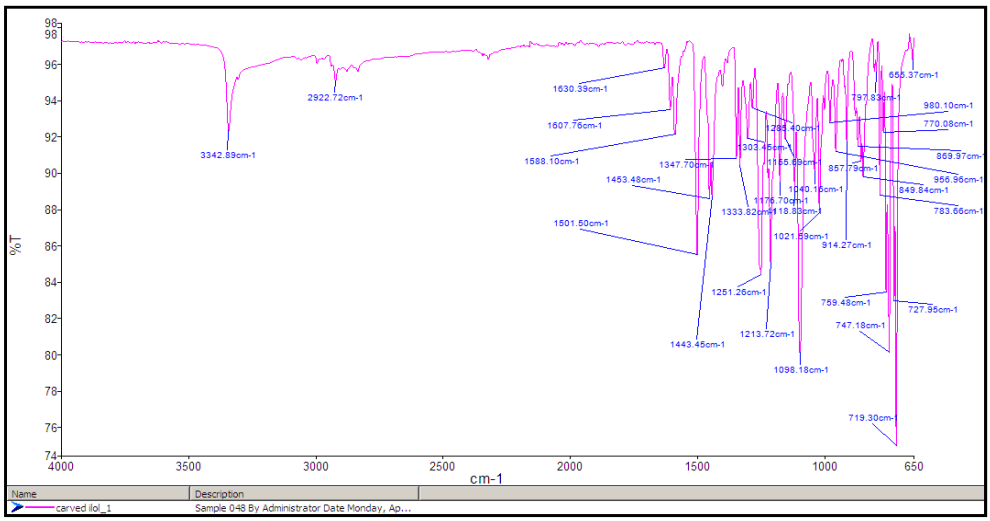

Fig. 6. FTIR of Carvedilol

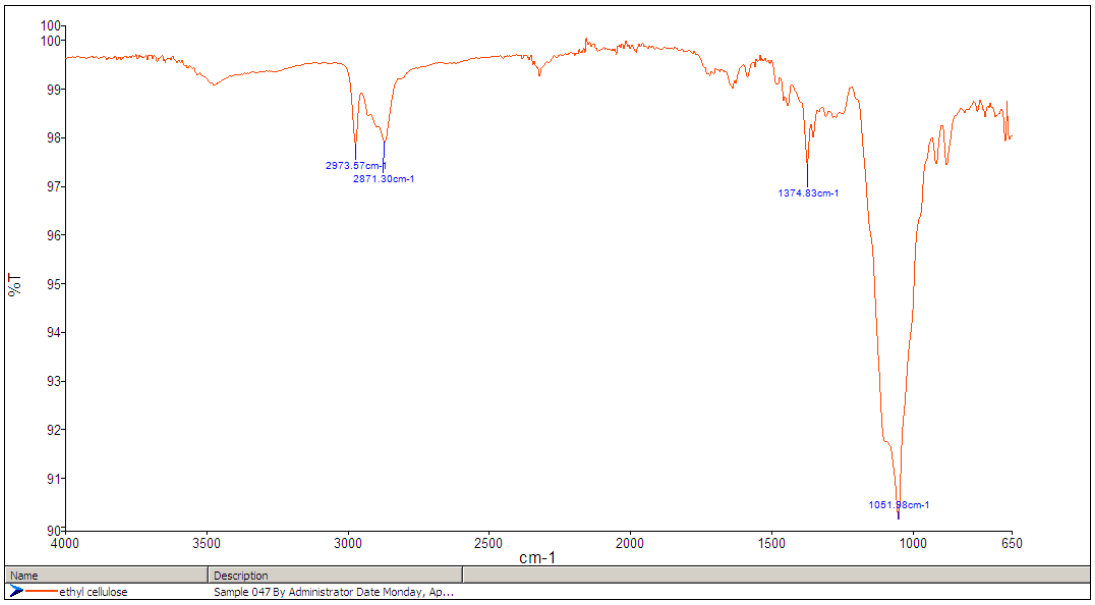

Fig. 7. FTIR of Ethyl cellulose

Table 3.Linearity plot of carvedilol in dichloromethane

CONCENTRATION(µg/ml)	ABSORBANCE
2	0.113
4	0.215
6	0.339
8	0.452
10	0.565

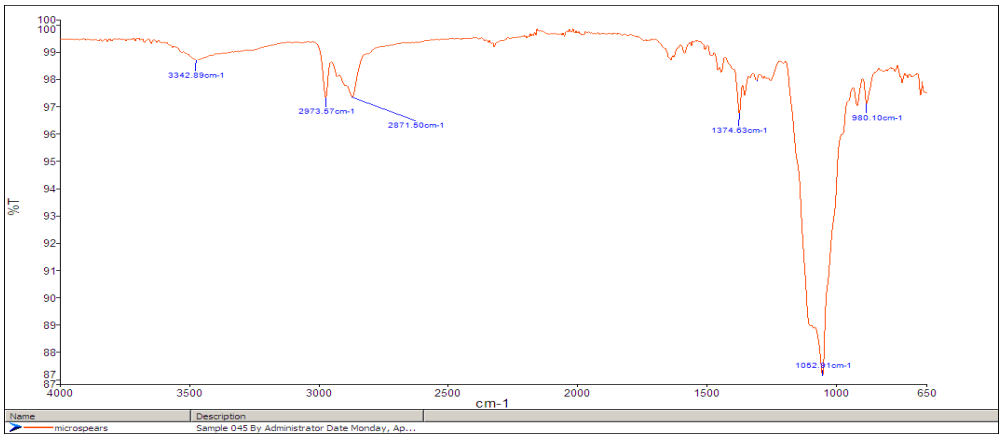

Fig. 8. FTIR of Microspheres

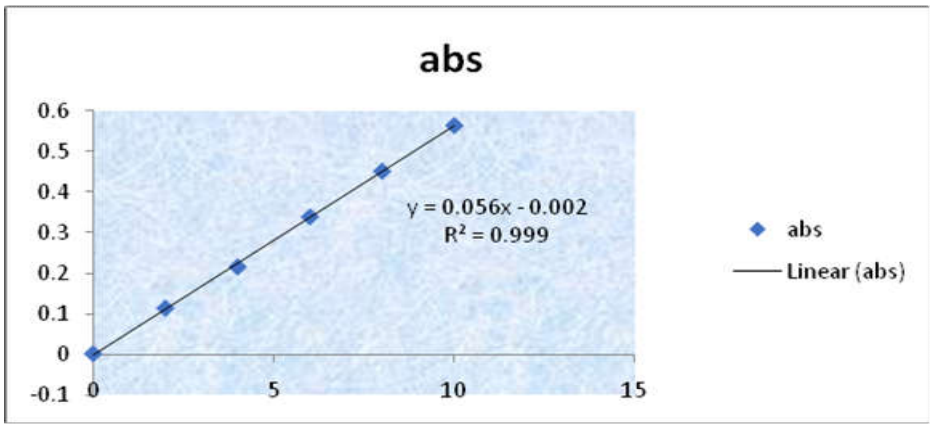

Fig. 9. Linearity plot of metformin hydrochloride

Table 4. Percentage yield, entrapment efficiency, drug loading of microspheres

Formulations	Percentage yield (%)	Entrapment efficiency(%)±SD	Drug loading±SD
F_1	61.6	62.6±0.378	81.14±0.0208
F_2	71.5	88.6±0.208	51.75±0.0152
F_3	73.6	97.5±0.1527	45.26±0.114

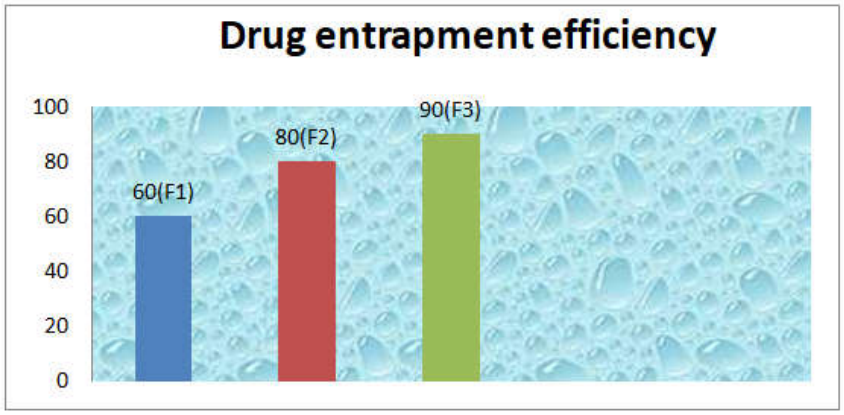

Fig. 10. Drug entrapment efficiency of microspheres

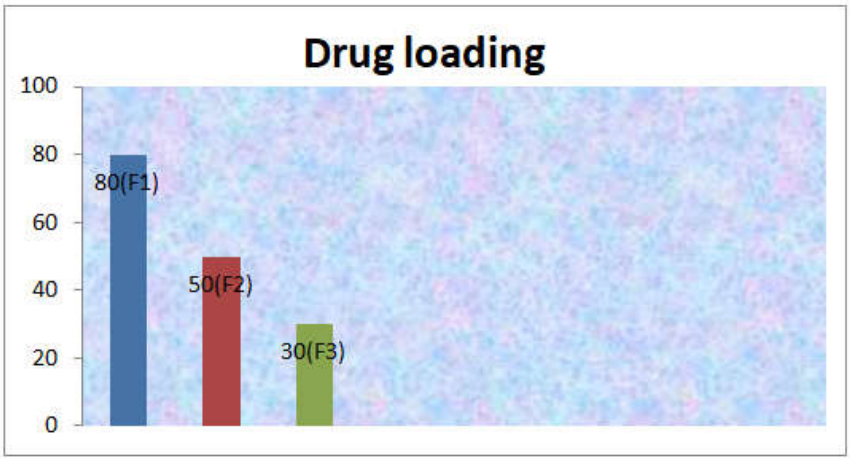

Fig. 11. Drug loading of microspheres

Table 5. Mean particle size of Carvedilol microspheres

S.No	Batches	Mean Particle Size(µm)
1	F_1	36.42
2	F_2	42.96
3	F_3	50.41

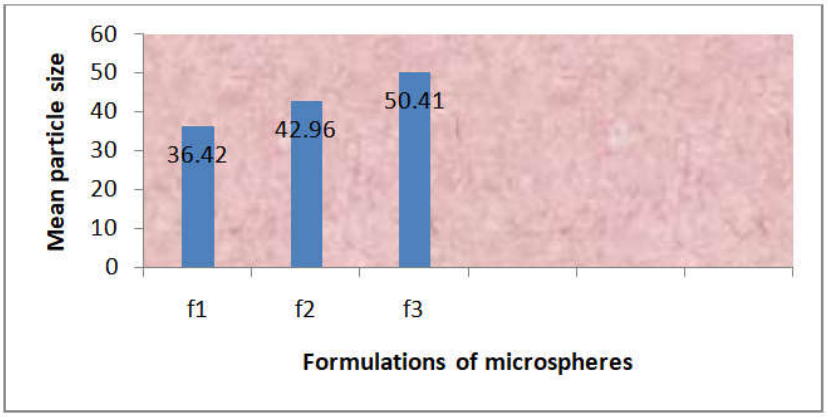

Fig. 12. mean particle size of microspheres

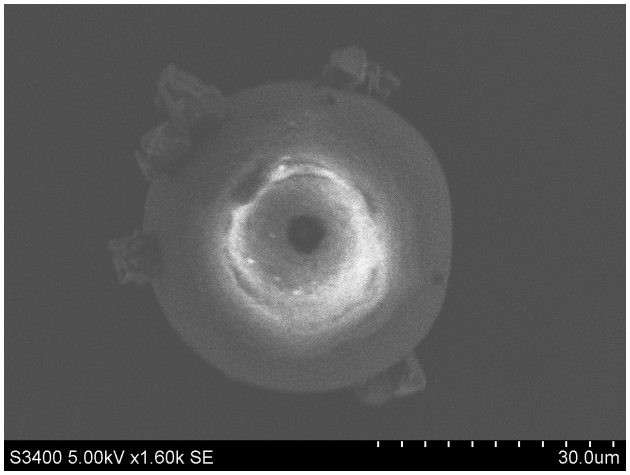

Fig. 13. SEM photograph of metformin hydrochloride microspheres

Table 6. Cumulative drug release of metformin hydrochloride microspheres

Time (hrs)	% Cumulative drug release		
	$F_{1\pm SD}$	$F_{2\pm SD}$	$F_{3\pm SD}$
0	0	0	0
1	18.14±0.012	14.5±0.102	13.67±0.01528
2	20.25±0.005	17.3±0.085	15.85±0.02517
3	24.35±0.068	19.28±0.342	17.25±0.03055
4	36.29±0.305	21.65±0.0643	19.54±0.03512
5	44.56±0.512	24.38±0.921	24.86±0.03055
6	52.72±0.482	32.59±0.007	27.62±0.1101
7	75.29±0.053	41.26±0.0181	33.86±0.09713
8	81.23±0.810	53.69±0.146	39.02±0.09849
9	82.45±0.035	71.34±0.0273	42.94±0.1
10	83.52±0.612	83.64±0.0471	54.37±0.283
11	-	84.5±0.0513	75.3±0.429
12	-	-	86.43±0.245

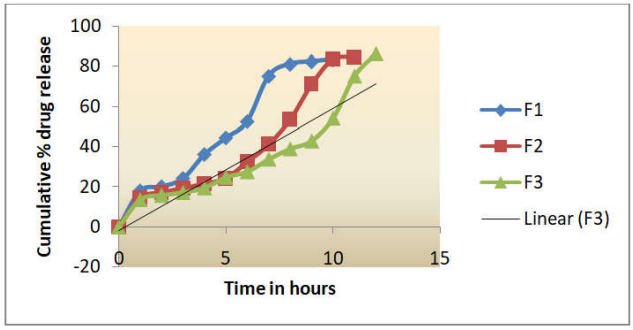

Fig. 14. In vitro drug release of metformin hydrochloride microspheres

Zero Order

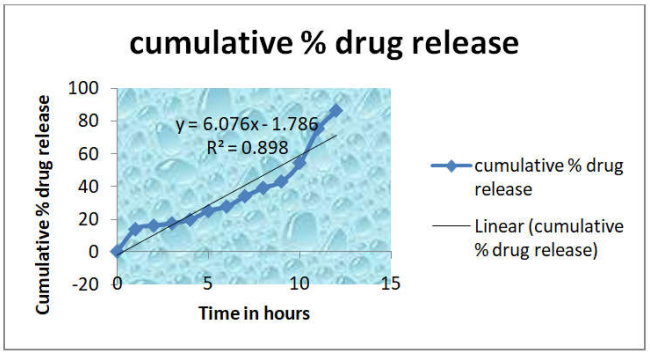

Fig. 15. zero order release of metformin hydrochloride microspheres.

Table 7. Zero order release model of metformin hydrochloride microspheres Optimized formulations

Time in hours(t)	cumulative %drug release(F_3)
0	0
1	13.67
2	15.85
3	17.25
4	19.54
5	24.86
6	27.62
7	33.86
8	39.02
9	42.94
10	54.37
11	75.3
12	86.43

First Order

Table 8. First order release model of metformin hydrochloride microspheresOptimized formulations

Time in hours	Log remaining cumulative %drug release(F_3)
0	0
1	1.1231
2	1.323
3	1.2334
4	1.14361
5	1.35550
6	1.55422
7	1.57660
8	1.59828

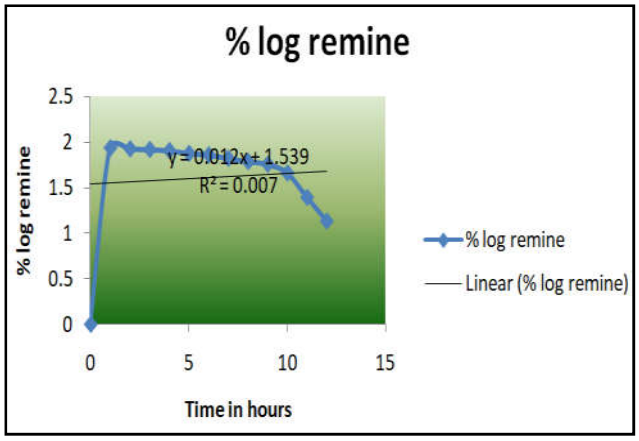

Fig. 16. First order release of metformin hydrochloride microspheres

Table 9. Higuchi release model of metformin hydrochloride microspheres
Optimized formulations.

Square root time	Log cumulative %drug release(F_3)
0	0
1	1.13576
1.414	1.20002
1.732	1.236781
2.036	1.13161
2.236	1.39550
2.449	1.44122
2.645	1.52960
2.828	1.59128
3	1.63286
3.162	1.73535
3.316	1.87679
3.464	1.93666

Higuchi Plot

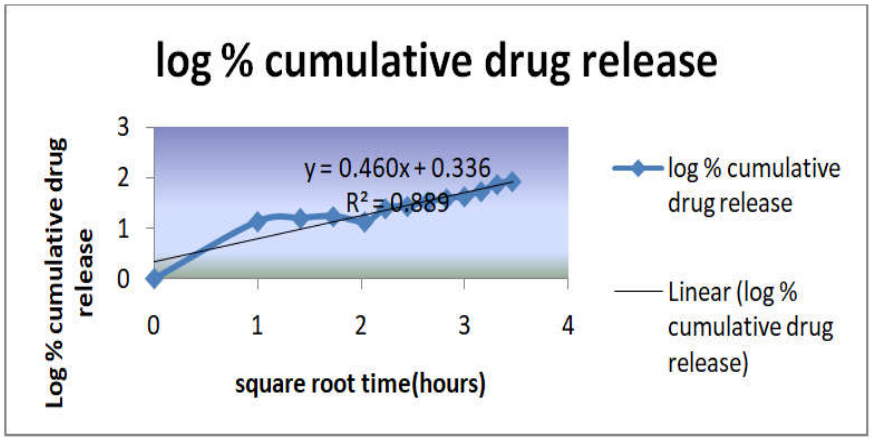

Fig. 17. Higuchi plot of metformin hydrochloride microspheres

Peppas Plot

Table 10. Korsmeyer-Peppas model for mechanism of drug release

Log time	Log cumulative %drug release(F_3)
0	0
0	1.13576
0.30102	1.20002
0.47712	1.23678
0.60205	1.13168
0.69897	1.39550
0.77815	1.44122
0.84509	1.52960
0.90308	1.59128
0.95424	1.63286
1	1.73535
1.04139	1.87679
1.07918	1.93666

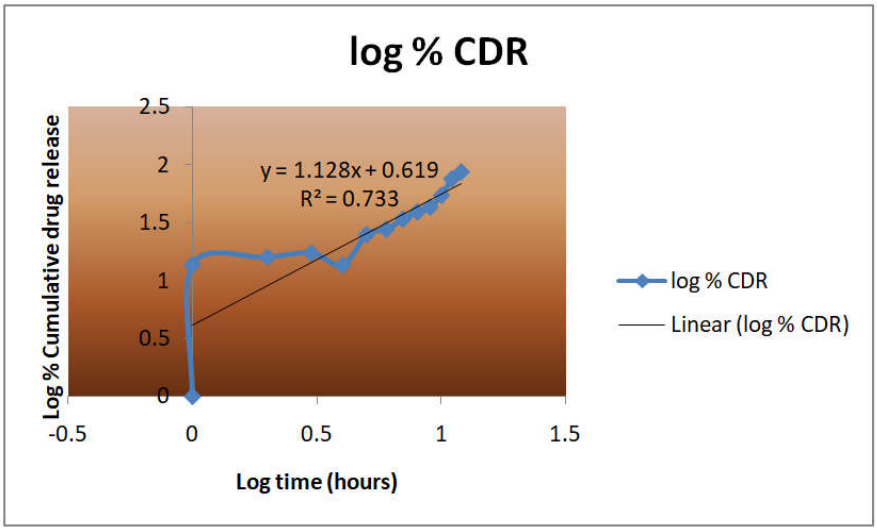

Fig .18. Peppas plot of metformin hydrochloride microspheres.

Table 11. Drug release kinetics of metformin hydrochloride microspheres

Formulations	Zero order	First order	Higuchi plot	Peppas plot(Korsmeyer)	
	R^2	R^2	R^2	R^2	N
F_1	0.963	0.000	0.897	0.719	0.909
F_2	0.927	0.001	0.907	0.742	0.713
F_3	0.898	0.007	0.889	0.733	0.549

Release Kinetics Plots for Ethyl Cellulose Microspheres Containing met form in hydrochloride

The dissolution of microspheres formulation follows Zero order and Higuchi models.

Summary and Conclusion

Mono or multi nuclear materials embedded in spherical coating matrix are called microspheres. Microspheres are solid, approximately spherical particles ranging in size from 1µm to 1000µm .These are made of polymeric, waxy or other protective materials, that are biodegradable synthetic polymers and modified natural products such as. Diabetes mellitus is a group of metabolic diseases characterized by high blood sugar (glucose) levels that result from defects in insulin secretion, or its action, or both. Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. The present work was designed to formulate Metformin hydrochloride microspheres by using ethyl cellulose polymer. Preformulation studies were done for bulk drugs. The Metformin hydrochloride microspheres were formulated and evaluated.

The ethylcellulose microspheres of Metformin hydrochloride were successfully prepared by solvent evaporation technique and confirmed that it is a best method for preparing Metformin hydrochloride loaded microspheres from its higher percentage yield. The formulation F3 has highest milligram of drug content followed by other formulations. The drug entrapment efficiency of three formulations were found to be F_1 62.6, F_2 88.6,F_3 97.5 and the percentage yield of three formulations were found to be F_1 61.6,F_2 71.55 and F_3 73.6. The particle size of a microsphere was determined by optical microscopy and all the batches of microspheres show uniform size distribution. The Mean particle size were found to be F_1 36.42,F_2 42.96,F_3 50.41. The prepared microspheres had good spherical geometry with smooth as evidenced by the scanning electron microscopy. The in vitro dissolution studies showed that Metformin hydrochloride microspheres formulation F3 showed better sustained effect over a period of 12hours. Dissolution results of formulations were found to be $F_1$83.52, $F_2$84.5 and $F_3$86.43 in which F_1 formulation shows maximum drug release at 10^{th} hour, F_2 at 11^{th} hour and F_3 at 12^{th}hour.

Hence the drug release of F_3 formulation gets sustained than other formulations for a period of 12 hrs. It was concluded that as the polymer concentration increases, density of polymer increases that results in increased diffusion path length, which the drug molecules have to traverse so, the drug release of F_3 formulation takes long time than other formulations. For all the formulations dissolution profile graph and percentage of drug release Vs time was plotted. From all the parameters mentioned above were taken, including surface characteristics of the formulation, drug polymer ratio and time F3 Shows the reliable results.

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