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FORMULATION DEVELOPMENT AND EVALUATION OF METFORMIN CONTROLLED RELEASE MICROSPHERES

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Abstract:
Micro particulate drug delivery system is one of the novel drug delivery system. Thus, it remains in the stomach without affecting gastric emptying rate for a prolonged period of time
Metformin is a novel anti- diabetic drug with elimination half-life 4.2 hours
Microspheres of metformin were prepared by emulsion solvent evaporation method by using HPMC, ethyl cellulose as polymers. The microspheres were evaluated for micromeritic properties, particle size, percentage yield, invitro buoyancy, incorporation efficacy, drug polymer compatibility (IR study), scanning electron microscopy and in-vitro drug release.
Results show that concentration of polymer increase effect of particle size, percentage yield, invitro buoyancy and invitro drug release. It was also found that cumulative drug release with grade HPMC. The micromeritic property was found to be good and scanning electron microscopy confirmed their spherical structure with smooth surface
Formulation F_2 prepared with HPMC, ethyl cellulose exhibited excellent micromeritic properties, percentage yield, invitro buoyancy, incorporation effiency and percentage drug release 99.76% for a period of 12 hours. The data obtained in this study thus suggest that microspheres of metformin are promising for sustained drug delivery, which can reduce frequency
Key words: *Metformin, Hydroxy propyl methyl cellulose, Ethyl cellulose, Microspheres*

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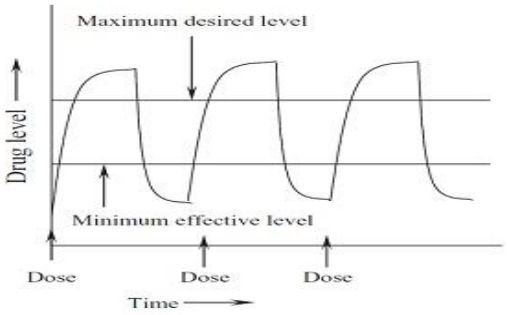
INTRODUCTION:

Microspheres are small spherical particles with diameters from 1 to 1000nm. In some cases, microspheres are also known as micro particles. Microspheres are produced from several natural and synthetic polymeric materials or even from inorganic materials. Microspheres are made up of continuous phase of one or more miscible polymer, in which the drug is completely dispersed at Macroscopic (particulates) or (dissolution level).
For example, microspheres are produced from commercially available polymers or ceramics.

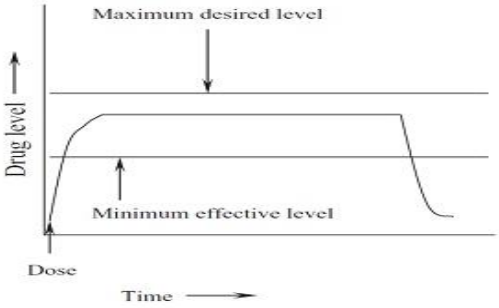
The polymer particles with inner surface and variable surface (smooth and porous to irregular and non-porous), are produced on a micron scale, capable of releasing a preloaded drug. The variety of methods for the production of microspheres offers a myriad of opportunities to control the aspects of administration of pharmaceutical compound. The release of desired amount of a component at the site of action and its reduction at non-targeted site.

Similarly, the factors focus specially for the protection of compounds before and after administration. Additionally, the vectorization of pharmaceutical compounds can be manipulated by coupling recognition of molecules to the microspheres.

The exploitation of these changes in pharmacokinetic behavior can lead to improved therapeutic effect. The main aim of any pharmaceutical compound administration system is to provide a therapeutic amount of the compound at the correct site in the body quickly to achieve tan effective concentration and then maintain for a given time. A well-designed modified release system for the compound can overcome some of the problems of conventional therapy and also improves the therapeutic efficiency, thus improving the patient's quality of life.



(a) traditional dosing of tablets



(b) controlled drug delivery system

DEFINATION:

Microspheres can be defined as solid spherical particles ranging from 1 to 1000nm, and they are made up of continuous phase of one or more miscible polymer, in which the drug is dispersed at macroscopic or dissolution level.

ADVANTAGES:

- Improves bioavailability
- Provides constant and prolonged therapeutic effect.
- Decreases dose and toxicity.
- It provides constant drug concentration in blood
- Reduces the dosing frequency and thereby improves the patient compliance.

DIS-ADVANTAGES:

- The cost is more.
- Reproducibility is less.
- The process conditions like change in temperature, PH, solvent addition, and evaporation may influences the stability of core particles.
-

APPLICATIONS:

- Microspheres are extensively used as diagnostics, for example, temperature-sensitive microcapsules for thermographic detection of tumors.
- It is also used for Hemoperfusion e.g.; activated charcoal.
- Microspheres also found in potential applications such as injection, or inhalational products.
- It is also mainly used for vaccine delivery to improve the antigenicity.
- It also plays a major role in drug targeting such as:

  Ocular- gelation with increased residence time.

  Intranasal- protein and peptide delivery.

  Oral.

- It also used for the encapsulation of microbial cells to increase the cell-loading capacity and the rate of production in bioreactors.
- It is instable towards environment (Oxygen, water) and volatility.
- It also helps in detoxification.

MATERIAL AND METHODS:

TABLE I: LIST OF MATERIALS

MATERIAL	VENDOM
Metformin	Chandra analytical lab, Hyderabad
Ethyl cellulose	MYL Chem. Mumbai
HPMC K100M	S.D. Fine chemicals
Eudragit	S.D. Fine chemicals
Acetone	S.D. Fine chemicals
Liquid paraffin	S.D. Fine chemicals
Calcium chloride	S.D. Fine chemicals
Span 80	S.D. Fine chemicals
Cellulose acetate	S.D. Fine chemicals

TABLE II: LIST OF EQUIPMENT

Instrument	Model/Company
Electronic Weighing Balance	Citizen, India.
Dissolution test Apparatus	Electrolab,TDMumbai,India.
UV/visible Spectrophotometer	Schimadzu UV-1601, japan
pH meter L I 120	Elico India Pvt Ltd, Hyderabad, India.
Magnetic stirrer	Citizen, India.
Pfizer hardness tester	Mansanto hardness tester
Centrifuge	Remi equipments, Mumbai
Glassware	Borosil
Microscope	Piolot products, Bombay
Sonitator	Remi instruments, Mumbai, India

STANDARD CALIBRATION CURVE OF METFORMIN:

Reagent: Standard stock-1mg/1ml in 7.4 Phosphate buffer

Determination of Beer's law Range and Plotting of Calibration Curve:

From working stock(2)solution, different aliquots of 0.5ml, 1ml, 1.5ml, 2ml, 2.5ml, 3ml, 3.5ml, 4ml, 4.5ml, and 5ml,were taken in genes of 10ml volumetric flasks and volume was made up with ph 7.4 phosphate buffer solution to get a sensor of working standard solution to get a sensor of working standard solution of concentration 5,10,15,20,25,30,35,40,45,and 50ug/ml, respectively

The solution was filtered through Whatman No.42 filter paper and the absorbances of samples are obtained spectrophotometrically against the reagent blank at 277 nm by using Elico UV-Visible spectrophotometer against ph 7.4 phosphate buffer as a blank and calibration curve was constructed. The procedure was repeated for 3hrs.

FORMULATION DEVELOPMENT OF METFORMIN MICROSPHERES:

Preparation of metformin microspheres by Emulsion Solvent Evaporation Method:

Microspheres containing (Metformin) drug were prepared by using drug and polymers in different concentrations. Polymers such as ethyl cellulose and HPMC are mixed with acetone upon mixing continuously until polymer gets dissolved. Then ass 75ml of liquid paraffin to the above solution and stir continuously at 100rpm until solvent get completely evaporated. Then, filter the solution with Whatman's filter paper and washed thrice with ether and air dry it. then, fuse along with calcium chloride. The optimum microspheres are obtained

SOLUBILITY PROFILE:

Solubility of Metformin was performed using different organic solvent and water

EVALUATION OF FORMULATED METFORMIN MICROSPHERES:

a) Tapered density:

It is the volume of powder determined by tapping by using a measuring cylinder containing weighed

amount of sample. The cylinder containing known number of microspheres was tapped for about 1 minute on a tapped density apparatus until it gives constant volume.

Tapered density = mass of microspheres/volume of microspheres

b) Bulk density:
It is defined as mass of powder divided by bulk volume.

Bulk density = weight of microspheres in grams/ bulk volume of microspheres

c) Carr's compressibility index: This is an important property in maintaining uniform weight.

Carr's compressibility index = tapered density-bulk density/ tapered density ×100

Lower the compressibility values indicate better flow.

Relationship between Carr's compressibility index and flow ability

Carr's compressibility index	Flow ability
5-15	Excellent
12-16	Good
18-21	Fair
23-28	Slightly poor
29-35	Poor
35-38	Very poor
>40	Extremely poor

d) Hausner's ratio:

Hausner's ratio = tapered density/ bulk density

Values less than 1.25 indicate good flow (= 20% Carr's index), whereas greater than
1.25 indicates poor flow (= 33% Carr's index).

e) Angle of repose:
Good flow properties are critical for the development of any pharmaceutical tablet, capsule or powder formulation. Angle of repose is defined as the maximum angle possible between the surface and the horizontal plane. It was determined by glass funnel method. Powders were weighed accurately and passed freely through the funnel so as to form heap. The height of the funnel was so adjusted that the tip of the funnel touched the apex of the heap. The diameter of the powder cone was measured and the angle of repose was calculated using following equation:

$$\tan\Theta = h/r$$

Where, θ = Angle of repose
h = Height of the pile.
r = Radius of the powder cone respective

Relationship between angle of repose and Flow ability

Angle of repose(ɵ)	Flow ability
<20	Excellent
20-30	Good
30-34	Passable
>40	Poor

f**) Particle size determination:**
Microsphere size was determined by using optical microscopic method with the help of ocular and stage micrometer. The sizes of around 100 particles were measured and their average particle size was determined.

The particle size of all the batches of the formulated microspheres in a sample was measured with an optical micrometre fitted with a calibrated eye piece. Calibration of the microscope was done prior to particle size measurement of the microspheres. The mean of 100 spheres was noted as particle size. All readings are average of three trials ± SD.

g) Percentage yield:
The prepared microspheres were collected and accurately weighed. The measured weight of prepared microspheres was divided by the total amount of all excipients and drug used in preparation of the microspheres, which gives the total percentage yield of floating microspheres.

Percentage yield = actual weight of product/ total weight of drug and excipients × 100

h**) Estimation of drug loading/ encapsulation efficiency**:
Microspheres weighing 200mg were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres and extracting the drug using pH 6.8 phosphate buffer (10ml). The extract was transferred to 100ml volumetric flask and volume was made up using pH 6.8 phosphate buffer. The solution was filtered and from the filtrate 10ml was taken and further

diluted to 100ml and the absorbance was measured at 275nm against pH 6.8 phosphate buffer as blank.

% drug entrapment efficiency = actual drug content/ theoretical content × 100

% drug loading = total weight of drug loaded in microspheres/ total weight of microspheres×100

(i) Percentage yield

Each batch of the formulated microspheres was weighed after drying in an oven. The weight of the collected microspheres was divided by the total weight of all the non-volatile components used for the preparation of the microspheres.

Percentage yield was calculated using the formula

Percentage yield = practical yield/ theoretical yield × 100

ENTRAPMENT EFFICIENCY

A weighed quantity of each batch of microspheres were crushed into powder and added to 100mL of phosphate buffer of pH 7.4. The resulting mixture was kept stirring at 1000rpm for 2 hours. Then the solution was filtered through membrane filter of 0.45 µm pore size and 5 ml of this solution was diluted to 50 ml using phosphate buffer of pH 7.4. After further suitable dilution, the samples were analyzed spectrophotometrically for the drug content at 272 nm. The drug entrapment efficiency was determined using the relationship.

Drug entrapment efficiency = experimental drug content/ theoretical drug content ×100

***IN VITRO* DRUG RELEASE STUDIES**

Drug release tests on each batch of the microspheres were carried out using a USP II **dissolution** rate test apparatus at a stirring speed of 100 rpm and temperature of 37 ± 0.5ºC. An amount of the microspheres equivalent to 100mg of Metformin was filled in a hard gelatin capsule (Size no.1) and was placed in the dissolution medium containing 500 ml of phosphate buffer pH 7.4. A 5mL quantity of the dissolution medium was sampled at predetermined time intervals, and fresh dissolution medium was simultaneously used to replenish the dissolution medium on each occasion to keep the volume constant. The sample was filtered through filter disc and the filtrate was diluted with fresh dissolution medium if necessary. The samples were analyzed using UV double beam spectrophotometer at 220 nm.

SCANNING ELECTRON MICROSCOPIC STUDIES

Examining the surface Metformin of a polymeric drug delivery system can provide vital information on the porosity and microstructure of these systems. The distribution and morphology of the surface of Metformin and the encapsulated matrix can also be directly observed. The most common technique used for characterizing the surface of Metformin morphology of drug delivery systems is Scanning Electron Microscopy (SEM). This method offers several advantages, by its versatility of the method, simplicity of sample preparation and ease of operation. The sample sizes, which can be analyzed using this method, range from nanometers to micrometers to centimeters. Sample prepared for this method should be sufficiently dehydrated since, a vacuum field is necessary for image generation in SEM. Prior to loading the samples for taking the photomicrograph, samples are coated (20-30nm in thickness) with electron-dense coating materials like gold, palladium or combination of both, to enhance the signal emitted by the sample by providing heavy metal atoms with incident beam of electron and, to conduct the accumulated sample charge and heat to the sample holder. The coating process is either carried through sputter-coating or thermal vacuum evaporation. The surface Metformin morphology of the formulated microspheres before and after dissolution studies was observed by SEM. The microspheres were placed on steel surface and coated with gold using an ion sputter and were observed at 10.0 KV.

RESULTS AND DISCUSSION:

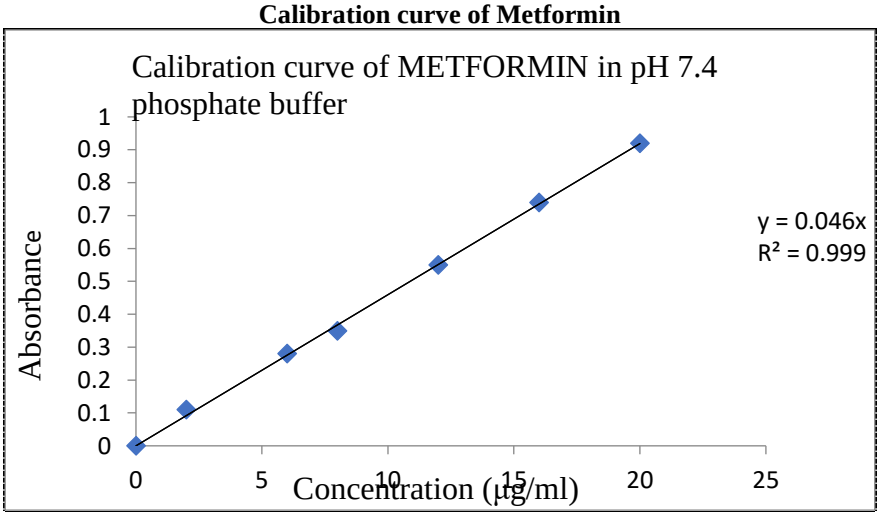
Metformin functional groups and their frequencies

Functional group	Absorbance cm^{-1}
C=Nstretching	1624.5
N-H stretching	3372.2 – 3132.76
C-N	1165.4

Calibration curve of Metformin in pH 7.4 Phosphate buffer.

Concentration (µg/ml)	Absorbance
0	0
2	0.110
6	0.283
8	0.352
12	0.552
16	0.744
20	0.922

Calibration curve of Metformin



Micromeritic propertic parameters of microspheres

Formulation	Bulk density (gm/cm^3)	Tapered density (gm/cm^3)	Carr's index (%)	Hauser's ratio (%)	Angle of repose (ɵ)
F1	0.16 ± 1.30	0.20 ± 1.70	20.0 ± 1.22	1.25 ± 3.11	19°03' ± 0.50
F2	0.44 ± 2.11	0.53 ± 2.12	16.9 ± 0.64	1.20 ± 1.82	17°01' ± 0.41
F3	0.42 ± 2.50	0.52 ±1.97	19.5 ± 2.12	1.24 ± 0.41	16°04' ± 0.19
F4	0.16 ± 1.21	0.19 ± 2.21	16.5 ± 4.78	1.18 ± 0.81	21°02' ± 1.80
F5	0.46 ± 4.10	0.54 ± 2.80	14.8 ± 2.15	1.21 ± 1.32	20°04' ± 0.21
F6	0.43 ± 2.84	0.52 ± 1.94	17.3 ± 1.83	1.17 ± 0.86	18°01' ± 1.31

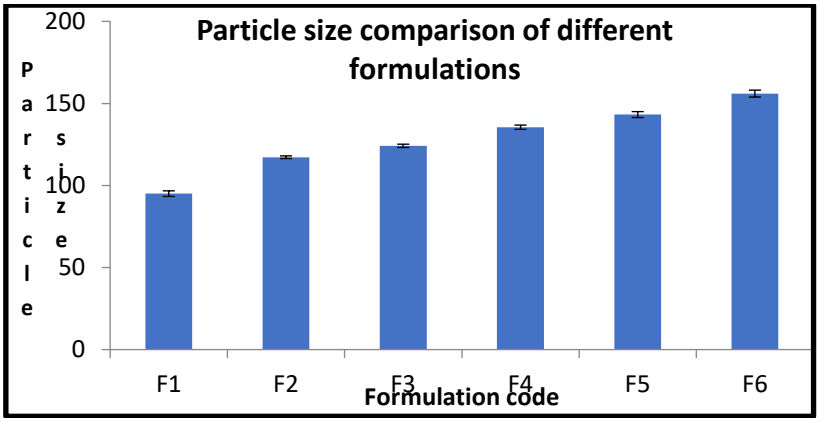
The values represent mean ± SD, n=3.

Mean particle size of different formulations of Metformin microspheres

Sr. no	Formulation code	Particle size (µ)
1	F1	95.03 ± 1.7
2	F2	117.21 ± 0.8
3	F3	124.17 ± 1.0
4	F4	135.51 ± 1.3
5	F5	143.21 ± 1.8
6	F6	156.01 ± 2.1

The values represents mean ± SD,n=3.

Mean particle size comparison of different formulations.

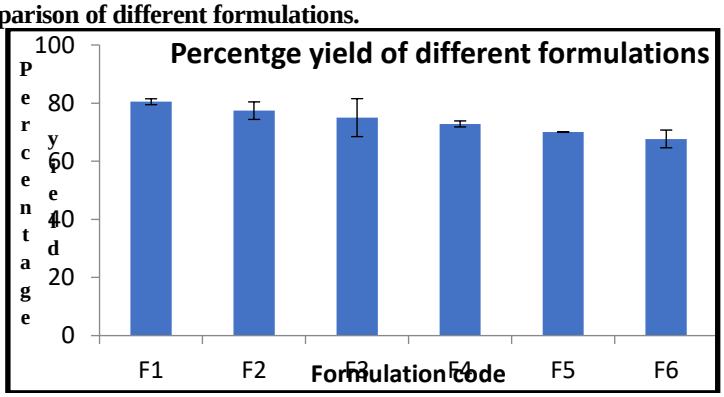


Percentage yield comparison of microspheres.

Formulation code	Practical yield	Percentage yield
F1	643.76 ± 0.12	80.47 ± 1.02
F2	696.90 ± 1.24	77.40 ± 3.01
F3	712.5 0 ± 0.21	75.00 ± 6.53
F4	728.00 ± 2.13	72.82 ± 1.04
F5	735.50 ± 2.11	70.05 ± 0.12
F6	744.48 ± 0.32	67.68 ± 3.06

The values represents mean ± SD, n=3.

Percentage yield comparison of different formulations.

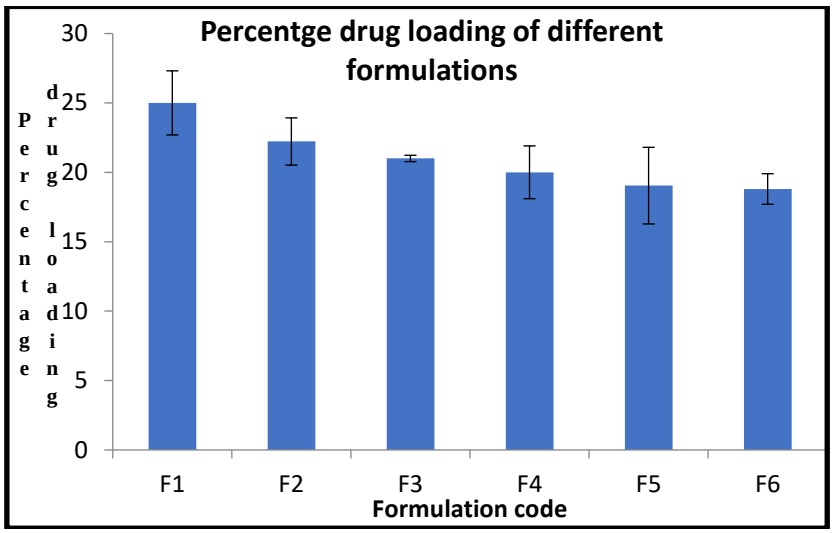


Percentage Drug loading and percentage Drug encapsulation of different formulations.

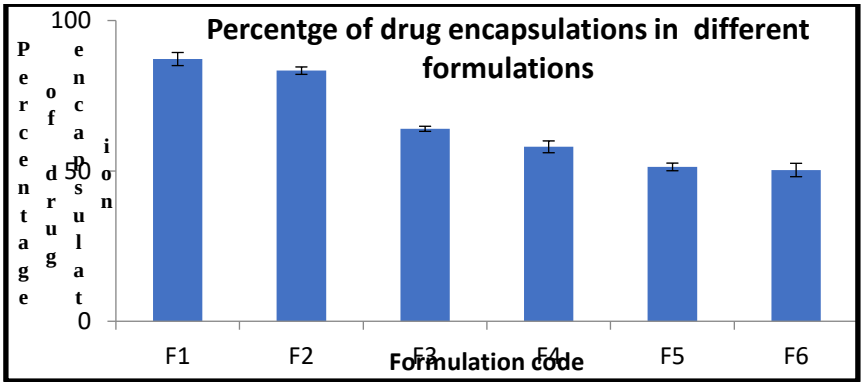
Formulation	%Drug loading	%Encapsulation efficiency
F1	25.00 ±2.31	87.20 ± 2.18
F2	22.22 ± 1.70	83.33 ±1.23
F3	21.0 0 ± 0.23	64.00 ± 0.85
F4	20.00 ±1.90	58.00 ±1.96
F5	19.04 ±2.76	51.33 ± 1.28
F6	18.18 ±1.10	50.30 ± 2.23

The values represents mean ± SD, n=3.

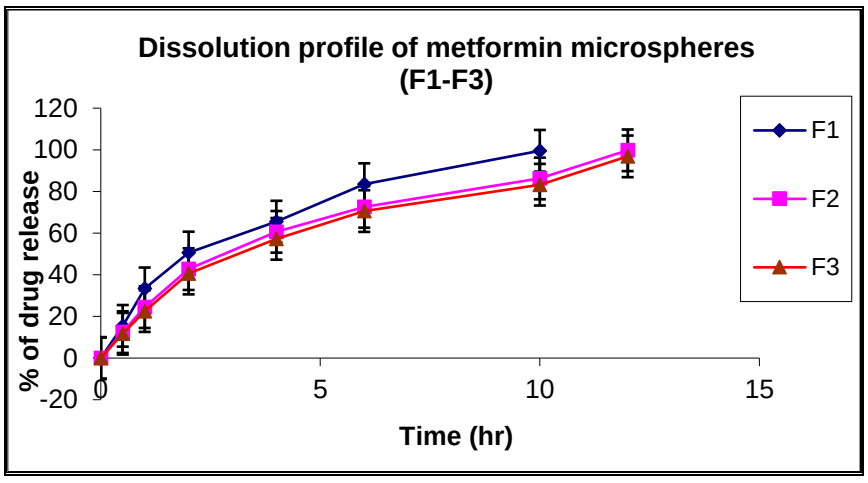
Comparison of percentage drug loading of different formulations.



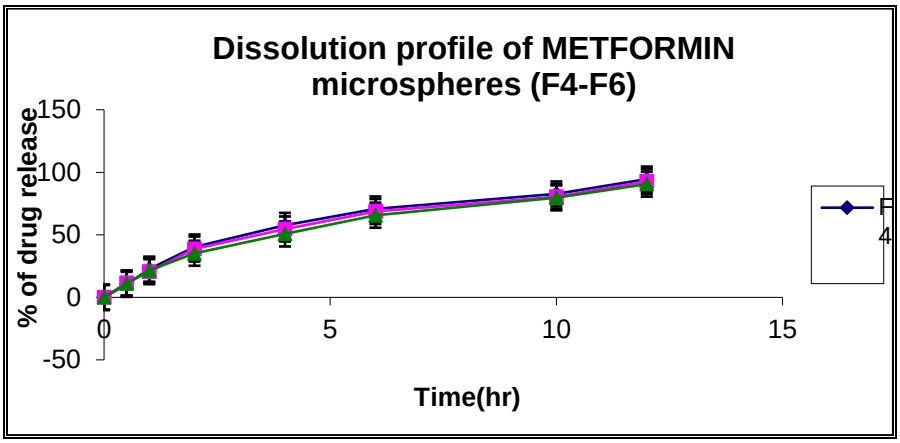
Comparison of % drug encapsulation of different formulations.



Cumulative % drug release Vs time for formulations F1 –F3.



Cumulative % drug release Vs time for formulations F1 –F6.



Cumulative % drug release Vs time for formulations F1 –F6

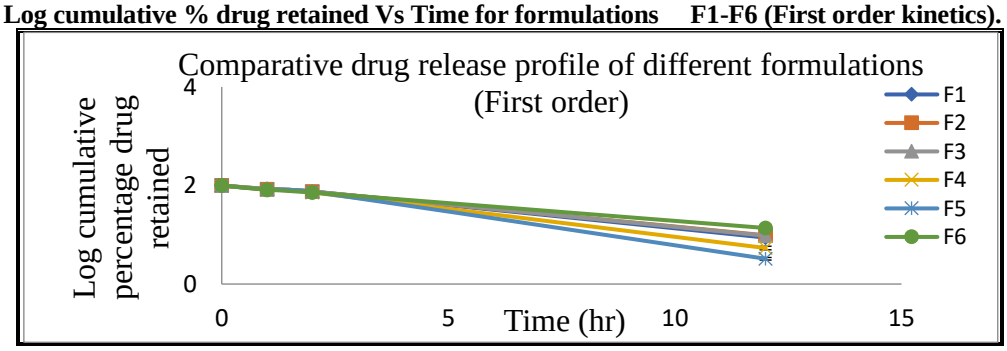
The values represent mean ± SD, n=3

Cumulative percentage drug release for F1-F6.						
Time (hr)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
0	0±0	0±0	0±0	0±0	0±0	0±0
0.5	15.02 ± 0.12	12.25 ± 1.01	11.45 ± 0.12	10.12 ± 0.42	10.15 ± 1.03	09.95 ± 0.12
1	33.30 ± 0.23	24.58 ± 2.01	23.56 ± 0.14	22.35 ± 0.32	20.25 ± 0.12	21.25 ± 1.08
2	50.03 ± 1.02	42.55 ± 0.32	40.65 ± 0.01	40.35 ± 0.11	38.14 ± 1.01	35.35 ± 1.03
4	65.21 ± 0.12	60.61 ± 0.21	57.25 ± 0.12	57.54 ± 0.05	54.65 ± 0.51	50.95 ± 0.08
6	83.12 ± 0.31	72.6 ± 0.53	70.58 ± 1.02	70.85 ± 0.23	68.55 ± 1.03	65.55 ± 1.06
10	99.9 ± 0.23	86.24 ± 0.21	83.25 ± 1.04	82.25 ± 0.12	80.15 ± 1.03	78.95 ± 0.32
12	-	99.95 ± 0.32	97.45 ± 0.03	94.15 ± 0.32	92.65 ± 0.12	90.54 ± 0.06

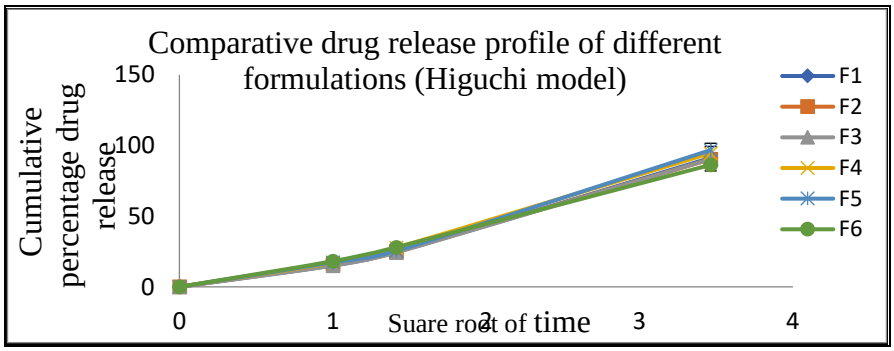
Model fitting release profile of formulations F1 to F6.

Formulation	**r^2 values**				
	Zero order	**First order**	**Higuchi matrix**	**Kroesmeyers peppas**	
				r^2	**n**
F1	0.943	0.903	0.969	0.912	0.452
F2	0.956	0.964	0.9774	0.903	0.516
F3	0.948	0.992	0.984	0.891	0.521
F4	0.944	0.909	0.986	0.923	0.512
F5	0.934	0.922	0.993	0.912	0.613
F6	0.930	0.992	0.993	0.962	0.632

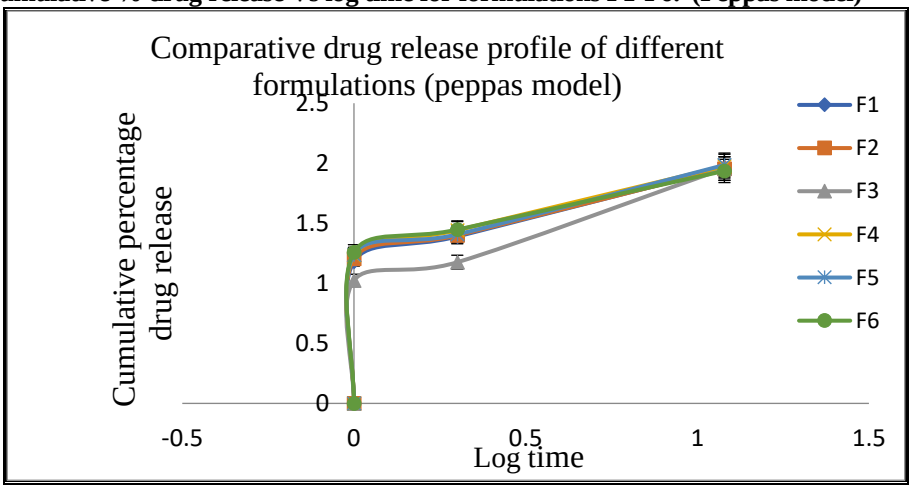
Plots of Log cumulative % drug retained Vs Time for formulations F1-F6 (First order kinetics).



Plots of cumulative % drug release Vs Sq. root time for formulations F1- F6. (Higuchi model)



Plots of log cumulative % drug release Vs log time for formulations F1-F6. (Peppas model)



Scanning electron microphotograph of floating microspheres of Metformin :

CONCLUSION:

- The present study has been a satisfactory attempt to formulate metformin microspheres, an orally administered anti-diabetic drug with a view of improving its oral bioavailability and giving a prolonged release of drug.
- controlled release microspheres with biocompatible polymer such as cellulose polymers such as Hydroxy propyl methyl cellulose (K100M) and Ethyl cellulose were successfully prepared by non-aqueous solvent evaporation method.
- Microspheres of different sizes and improved drug entrapment efficiency could be obtained by varying the drug to polymer concentrations. The formulations showed good flow properties, suggesting that, in future they could be easily and successfully packed and developed into a capsule dosage form.
- This study has suggested that sustained microspheres could be a candidate novel drug delivery device to improve the bioavailability of drug.
- Thus the prepared microspheres proved to be a potential candidate as a micro particulate sustained release drug delivery device in this era of patenting novel and controlled release formulations

REFERENCES:

1 . Block LC, Schemling LO, Couto AG, Mourao SC, and Bresolin TMB, Pharmaceutical equivalence of metformin tablets with various binders, Journal of Applied Pharmaceutical Science, 2008, 29(1), 29–35, 11. Sharma VK and Bhattacharya A, Release of metformin hydrochloride from Ispaghula-sodium alginate beads adhered on cock intestinal mucosa, Indian Journal of Pharmaceutical Education and Research, 2008,42(4), 363–370,.

2. Das MK, Rao KR. Evaluation of zidovudine encapsulated ethyl cellulose microspheres prepared by water-in-oil-in-oil (w/o/o) double emulsion solvent diffusion technique. Acta Poloniae Pharmaceutica - Drug Research 2006; 63(2): 141-148

3. Carnali JO, Naser MS. The Use of Dilute Solution Viscosity to Characterize the Network Properties of Carbopol Microgels. Colloid and Polymer Science 1992; 270(2): 183-193

4. Mishra B, Jayanth P, Sankar C. Development of chitosan-alginate microcapsules for colon specific delivery of metronidazole. Indian Drugs 2003; 40(12): 695-700

5. Dubey RR, Parikh RH. Two stage optimization process for formulation of chitosan microspheres. AAPS Pharm Sci Tech 2004; 5(1), Article 5

6. Choudary PK, Kar M. Preparation of alginate gel beads containing metformin hydrochloride using emulsion-gelation method. Tropical Journal of Pharmaceutical Research 2005; 4(2): 489-493

7. Zessin G, Dashevsky A., The effect of viscosity on micromeritic properties of ethyl cellulose-walled theophylline microspheres. 1995 Proc. 1st World Meeting APGI/APV, Budapest, pp. 443- 444, May 9-11.

8. Lachman L, Lieberman HA, Kanig JL. The theory and practice of industrial pharmacy, 4th ed. Mumbai Varghese Publishing House 1991; pp 183-184

9. Martin A, Bustamante P, Chun AHC. Physical Pharmacy: Physical chemical principles in the pharmaceutical sciences, 4th ed. B.I. Publications Pvt. Ltd. 2005; pp 423-448

10. Sengel CT, Hascicek C, Gonul N. Development and in-vitro evaluation of modified release tablets including ethylcellulose microspheres loaded with diltiazem hydrochloride. J Microencapsulation 2006; 23(2): 135-152

11. Bhagwat DA, Bhutkar MA, Todkar SS, Mohite SK, Gattani YS. Formulation and evaluation of controlled release microspheres of isosorbide dinitrate. Int J Pharm Tech Res 2009; 1(2): 125-128

12. Khan SA, Ahmad M, Murtaza G, Aamir MN, Rehman N, Kousar R, Rasool F, Akhtar M. Formulation of Nimesulide Floating Microparticles Using Low-viscosity Hydroxypropyl Methylcellulose. Trop J Pharm Res 2010; 9 (3): 293-299

13. Vasir JK, Tambwekar K, Garg S. Bioadhesive microspheres as a controlled drug delivery system, Int J Pharm 2003; 255: 13-32