International Journal of Farmacia

Journal Home page: www.ijfjournal.com

ISSN: 2455-8109

Formulation and in-vitro evaluation of metformin hydrochloride microspheres by solvent evaporation technique

Sangi Pushpalatha[1*],N.Sriram[2]

[1]Vignan Institute of Pharmaceutical Sciences, DeshmukhiVillage,YadadriBhuvanagiriDist
[2]Holy Mary Institute of Science and Technology(College Of Pharmacy) Bogaram(V),Keesara (M) Dist-501301

Corresponding Author: SangiPushpalatha

[*]E-mail: pushpalatha.latha6@gmail.com

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. 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.

Keywords: Microspheres, Microencapsulation, Microcapsules, Biodegradable polymers.

INTRODUCTION

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.

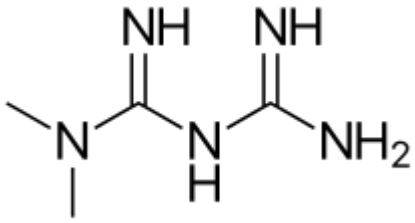
Different kinds of controlled drug delivery systems have been developed for various routes of administration, since they require less frequent drug administration, provide more efficient therapeutic effects, and reduce the incidence of side effects. To develop a drug delivery system for oral administration, the preferred route of administration, it is necessary to optimize the release rate of an active ingredient from the system. One of the most

extensively studied methods is microsphere formulation.

In case of Diabetes mellitus needs to deliver the drug in controlled manner. To achieve this microspheres may be a promising drug delivery.

DRUG PROFILE

COMMON BRAND(S): Glucophage
GENERIC NAME(S): Metformin



Iupac Name N,N-DimethylimidodicarbonimidicDiamide

CAS number 657-24-9
Chemical formula: $C_4H_{11}N_5$
Molar mass**:** 129.1636 g/mol

METHODS OF PREPARATION OF MICROSPHERES

Different types of methods are employed for the preparation of microspheres. They include,

- Solvent evaporation.
- Single emulsion method.
- Double emulsion method.
- Polymerization technique.
- Phase separation co-acervation technique.
- Spray drying and spray congealing.
- Solvent removal.
- Solvent extraction.
- Freeze drying.
- Chemical and thermal cross linking.
- Precipitation.
- Hot melt microencapsulation method.

POLYMERS IN THE PREPARATION OF MICROSPHERES

Synthetic polymers

- Non-biodegradable polymers: Poly methyl methacrylate (PMMA), Acrolein, Glycidyl methacrylate, Epoxy polymers.
- Biodegradable polymers :Lactides, Glycolides& their co polymers, Poly alkyl cyano acrylates, Poly anhydrides.

Natural polymers

- Proteins:Albumin, Gelatin, and Collagen
- Carbohydrates: Agarose, Carrageenan, Chitosan, Starch
- Chemically modified carbohydrates:Poly dextran, Poly starch

LOADING OF DRUG

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

1. During the preparation of microspheres .
2. 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.

MATERIALS AND METHODS

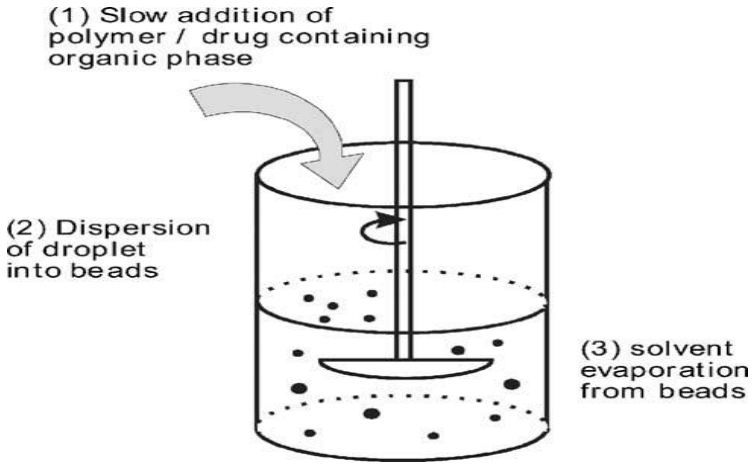
Materials

S.No	Chemicals	Supplied by
1.	carvedilol	Gift sample from Chandra labs, Hyderabad.
2.	Ethyl cellulose	Research-lab fine chem. industries, Mumbai.
3.	Dichloro methane	Research-lab fine chem. Industries, Mumbai.
4	Poly vinyl alcohol	Research-lab fine chem industries Mumbai.
5	Ethanol	Changshuyangyuanchemicalscorp.china.

Formulation table of metformin hydrochloride microspheres

Solvent evaporation method

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.

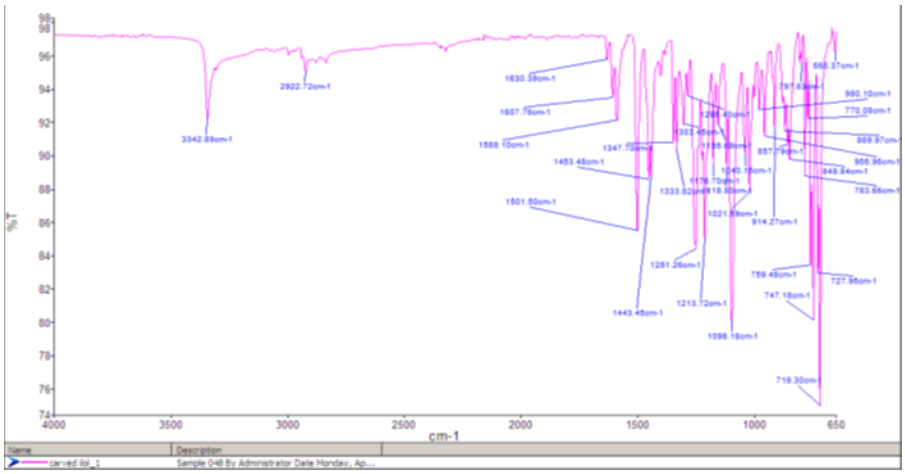


RESULTS AND DISCUSSION

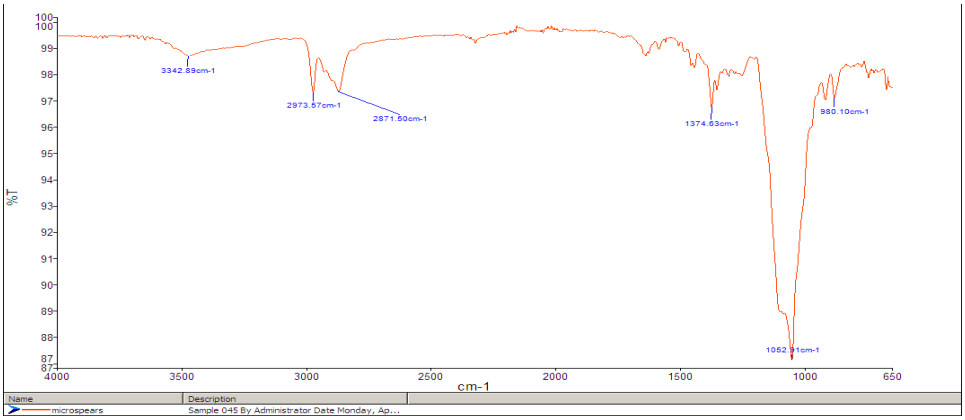
Drug and Excipients Compatibility Studies

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 andpolymer.



FTIR of Carvedilol

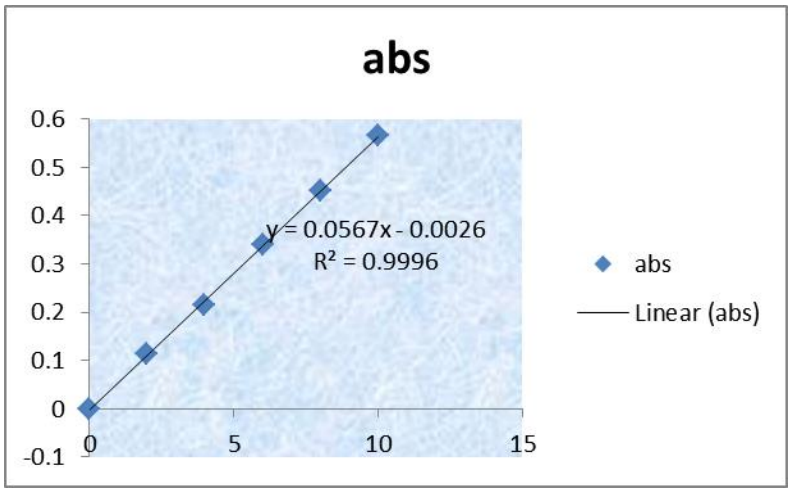


FTIR of Microspheres

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 standard graph between concentration Vs absorbance was given in figure

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

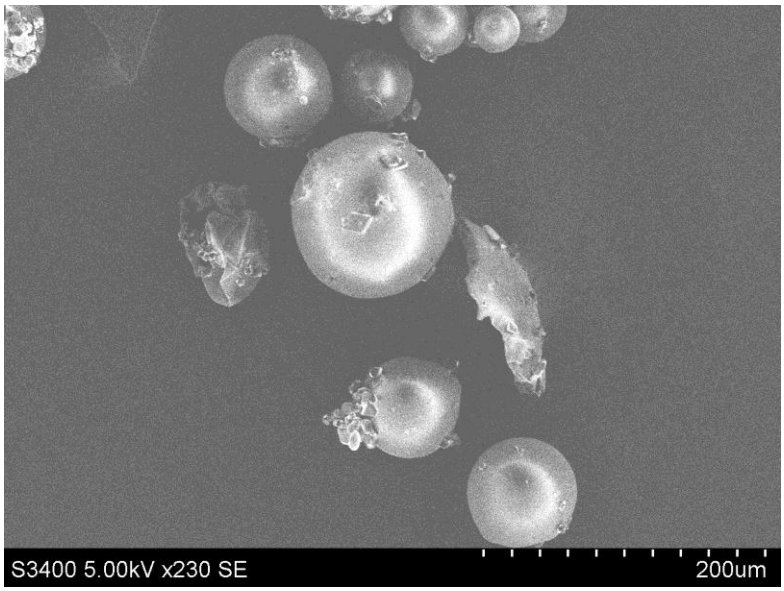


Percentage yield, entrapment efficiency, drug loading of microspheres

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

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.

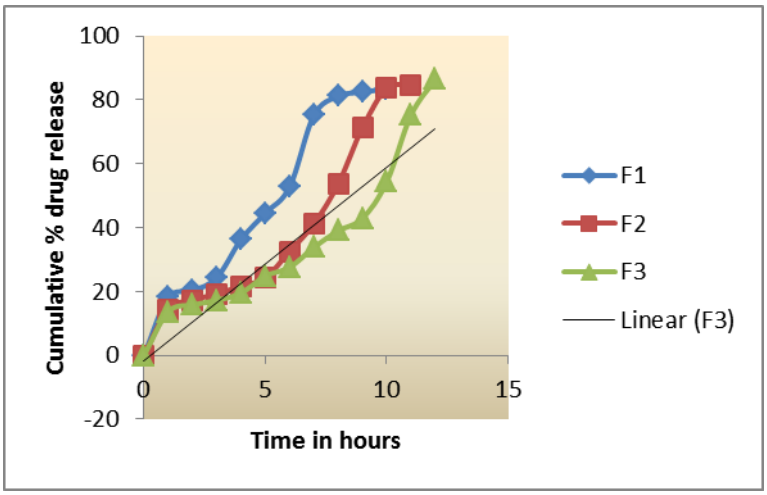


SEM photograph of metformin hydrochloride microspheres

In-vitro release studies: The in-vitro release profile of metformin hydrochloridemicrospheres were conducted in ph buffer for 12 hours.

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

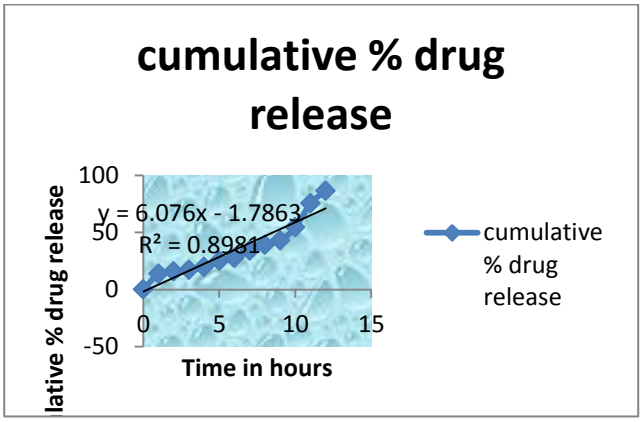


Release Kinetics Plots For Ethyl Cellulose Microspheres Containing metformin hydrochloride

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

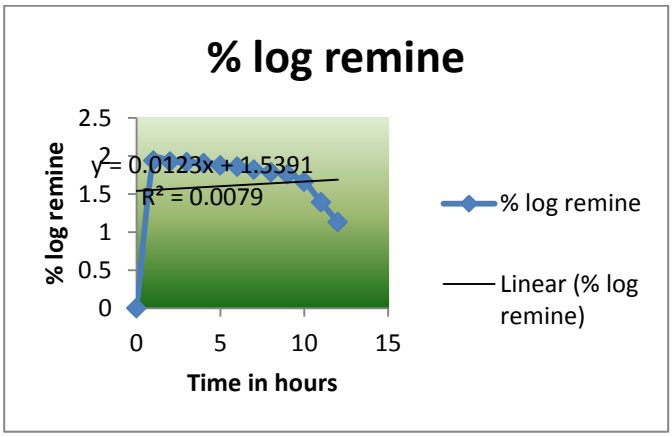
Zero order release model of metformin hydrochloride microspheres Optimized formulations.

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



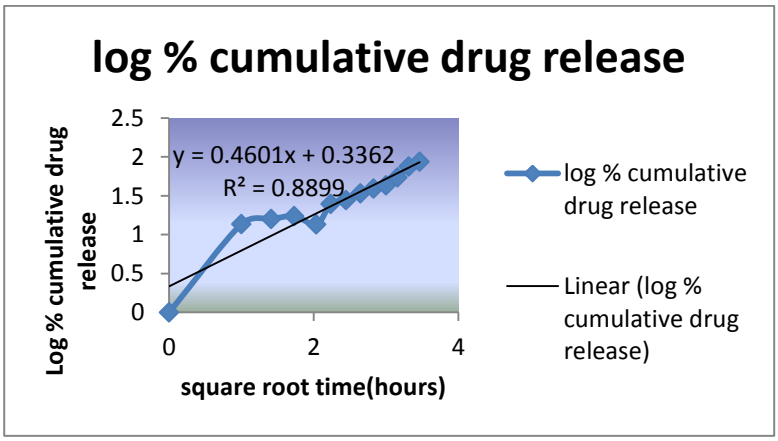
Zero order release of metformin hydrochloride microspheres

First order

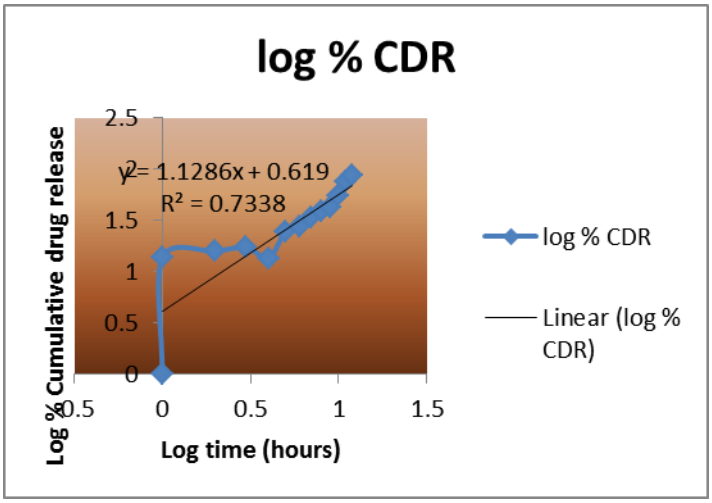


First order release of metformin hydrochloride microspheres.

Higuchi Plot



Higuchi plot of metformin hydrochloride microspheres.



peppas plot of metformin hydrochloride microspheres

CONCLUSION

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.

Dissolution results of formulations were found to be $F_1$83.52,$F_2$84.5and$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.

REFERENCES

[1]. European pharmacopeia 2 (5), 2005, 909-911.

[2]. Ei –Bagory , Ibrahom M, Hosney , E.A.AL- suwaych .s, Mahrous G M effect of spheres size, polymer to drug ratio and plastisizer concentration on the release of theophilin from ethyl cellulose microspheres , Saudi pharm Journal 15, 2007, 213-216.

[3]. Encyclopedia of pharmaceutical technology, 10, 1998, 1-30.

[4]. Jaspreetkaurvasir, kaustubhtambwekar, sanjay gang Bio adhesive microspheres as controlled drug delivery system, International journal of pharmaceutics. 255, 2003, 13-32.

[5]. Perumal D. microencapsulation of Ibuprofen and Eudragit RS 100 by solvent diffusion technology , International journal of pharmaceutics. 218, 2001, 1-11.

[6]. Patrick B O Donnell, James W McGinity, preparation of microspheres by solvent evaporation technique , Advanced drug delivery review, 28, 1998, 25-42.

[7]. Edith Mathiowitz (Edited by), Encyclopaedia of Controlled Drug Delivery, Second volume.

[8]. Wakode RR, Bajaj AN, Formulation and characterization of pramipexole loaded microspheres, 2008.

[9]. Targeted and controlled drug delivery by S.P Vyas ,R.K.Khar ;425-441.

[10]. Yie W. Chein, Novel Drug Delivery Systems, Second Edition, Revised and Expanded, Marcel Dekker, INC. New York, Basel, Hong Kong, 139-196.

[11]. Joseph R. Robinson, Vincent H. L. Lee, Controlled Drug Delivery fundamental & applications, Second Edition, Revised and Expanded, Marcel Dekker, INC. New York, 581-590.

[12]. Ehret GB, Munroe PB, Rice KM, et al. (October 2011). "Genetic variants in novel pathways influence diabetes mellitus". Nature 478 (7367): 103–9. doi:10.1038/nature10405. PMID 21909115.