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PREPARATION AND EVALUATION OF ALBUMIN MICROSPHERES CONTAINING METFORMIN HYDROCHLORIDE BY THERMAL METHOD

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ABSTRACT:

Microspheres are sometimes referred as micro particles. Microspheres form homogeneous, monolithic particles which improve the treatment by providing localization of the drug at the site of action and by prolonging the drug release. Microspheres are small spherical particles, with diameters in the micrometer range typically 1 μm to 1000 μm. The objective of the present study was to formulate sustained release microspheres of Metformin hydrochloride (MTH) using egg albumin as release retarding agent. From FTIR studies it was conformed that no interactions were found between MTH and polymers. The maximum yield of the microspheres was found to be 98.87% and the encapsulation efficiency was found to be 64.7%. The prepared albumin microspheres released the drug completely within 7 hours at lower drug to polymer ratio. At ratio of more than 1:2, the drug release was sustained over a period of 10 hours. The microspheres were discrete, spherical and uniform in shape. The particle size was of the microspheres was found to be 99.6 μm.

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The prepared microspheres showed minor changes in particle size only under stability study with no appreciable change in drug content proving good stability of the product conducted in accelerated condition. The present study signifies the utility of microspheres in retarding the drug release. This may in turn reduces the frequency of dosing, thereby improving the patient compliance.

Keywords: Microspheres, Metformin hydrochloride (MTH), Albumin, Denaturation.

1. INTRODUCTION:

Microspheres are homogeneous, monolithic particles which improve the treatment by providing localization of the drug at the site of action and by prolonging the drug release [1]. Polyethylene, polystyrene and expandable microspheres are the most common types of polymer microspheres [2]. The goal of any drug therapy is to achieve the desired drug concentration in blood which is therapeutically effective over an extended period of time. This can be achieved by proper design of sustained release dosage regimen [3]. Metformin hydrochloride is a very widely accepted drug as it does not induce hypoglycemia at any reasonable dose. In type II diabetes, metformin is drug of choice alone or in combination with other hypoglycaemic agents. In spite of its favourable clinical response and lack of significant drawbacks, chronic therapy with metformin hydrochloride suffers from certain specific problems of which, the most prominent being the high dose (1.5-2.0 g/day), low bioavailability (60%) and high incidence of GI side effects (30% cases). The low bioavailability and short half-life of metformin hydrochloride make the development of sustained-release forms desirable [4]. Microencapsulation is one of the novel methods for retarding drug release from dosage forms and minimizing the adverse effects thereby increasing the patient compliance [5]. Heat denaturation is one such microencapsulation method that can be used to coat a drug with a polymer for sustaining the drug release [6]. The mechanism of drug release from microspheres can occur either by diffusion where on contact with aqueous fluids in the gastrointestinal tract (GIT), water diffuses into the interior of the particle causing drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior or it may occur either by erosion where coatings can be designed to erode gradually with time, thereby releasing the drug contained within the particle or by osmosis by allowing water to enter under the right circumstances, an osmotic pressure can be built up within the interior of the particle. The drug is forced out of the particle into the exterior through the coating [7-8]. The objective of the present study was to

formulate sustained release microspheres of Metformin hydrochloride (MTH) using egg albumin as release retarding agent.

2. MATERIALS & METHODS:

2.1. Materials

MTH was procured from Matrix Laboratories, Bangalore. Egg Albumin and Sodium carboxy methyl cellulose was purchased from S.D. Fine chemicals, Mumbai., India. Chloroform, Methanol and Dichloromethane were purchased from Merck Ltd.

2.2. Methods

Preparation of calibration curve

A calibration curve for metformin hydrochloride was established by using hydrochloric acid buffer of pH 2.2. 12 A plot of absorbance vs. concentration was obtained. Dilutions were prepared from stock solution to contain 4, 8,12,16,20, 24, 32 µg/ml.

Preparation of Microsphere:

Albumin microspheres were prepared by heat denaturation method. A solution of albumin (1 g in 25ml) was prepared and the drug of weight 1gm was added to the albumin solution. The contents were slowly added to a beaker containing 100 ml of preheated 60C liquid paraffin containing Tween 80 as emulsifying agent and stirred for 1hr. The temperature was reduced to 40C for hardening process and was maintained for 25min.The resulting microspheres were stabilized using gluteraldehyde solution (25%v/v) for a period of 15min. The microspheres were collected by decantation and washed with n-hexane and dried at room temperature. The microsphere formulations were carried out in different ratio as per the Table1.

Table 1: Composition of formulations of TH and albumin microsphere

Formulation Code	Drug-Polymer Ratio	
	Metformin hydrochloride (MTH)	Egg Albumin
F1	1	1
F2	1	1.5
F3	1	2
F4	1	2.5
F5	1	3
F6	1	4
F7	1	5

EVALUATION OF MICROSPHERES:

Drug Polymer Interaction Studies:

Drug-polymer interactions were studied by FTIR spectroscopy. The spectra were recorded for MTH and physical mixture of MTH: albumin (1:1). Samples were prepared in KBr disks (2 mg sample in 200 mg KBr) with a hydrostatic press at a force of 5.2 τ cm-2 for 3 minutes. The scanning range was 400–4000 cm-1and the resolution was 4cm-1.

Surface morphology:

The microspheres were coated with gold vacuum at high voltage (800-1500V) using ion coater. Samples were examined with scanning electron microscope.

Micromeritics properties:

The average particle size of the microspheres was determined by using optical microscope. The flow properties and packing properties were investigated by measuring the angle of repose, tapped density and bulk density [9].

Drug entrapment:

Accurately weighed microspheres equivalent to 200mg of drug was suspended in 25ml of methanol and sonicated for 3 mins. The solution was then filtered, diluted suitably and analyzed for drug content spectrophotometrically at 272nm. The percentage drug entrapment was calculated as,

% Drug Entrapment = (Practical drug loading/ Theoretical drug loading) X 100

Dissolution studies:

Dissolution test was performed in USP XXIII dissolution test apparatus by paddle method. The dissolution media used was 900ml of phosphate buffer pH 7.4 maintained at 37±0.5C and rotated at 100 r/min. Aliquots samples were withdrawn at specified time intervals and replaced with same volume of fresh media, filtered and analyzed spectrophotometrically (Shimadzu 1600) at 272nm for cumulative drug release. Results are given in table3.

Stability Studies:

The stability protocol was designed based on the ICH ‘Q1AR2’ guidelines. The microspheres formulations chosen were stored at 30 ± 20 C and 65 ± 5% RH for a period of 6 months and at 40 ± 20 C and 75 ± 5% RH for a period of 6 months. The stored samples were tested for their drug content and for any physical change. The testing was carried out at 0, 2, 4 & 6 months for accelerated storage condition as given below [10].

Microspheres Formulation	Days (0)	Days (60)	Days (120)	Days (180)
F5	98.87	98.73	98.85	98.97

Kinetics of Drug Release:

Different mathematical models may be applied for describing the kinetics of the drug release process from the formulation matrix; the most suited being the one which best fits the experimental results. The kinetics of TH release from tablets was determined by finding the best fit of the dissolution data (drug release *vs.* time) to distinct models: Zero order [eq.1], first-order [eq.2] and Higuchi [eq. 3].

$$Qt = k_0 t \qquad [1]$$

$$Qt = Q\infty (1-e^{-k1t}) \qquad [2]$$

$$Qt = k_H t^{1/2} \qquad [3]$$

Where Q∞ being the total amount of drug in the matrix, k0 the zero order kinetic constant, k1 the first order kinetic constant and KH representing the Higuchi rate constant.

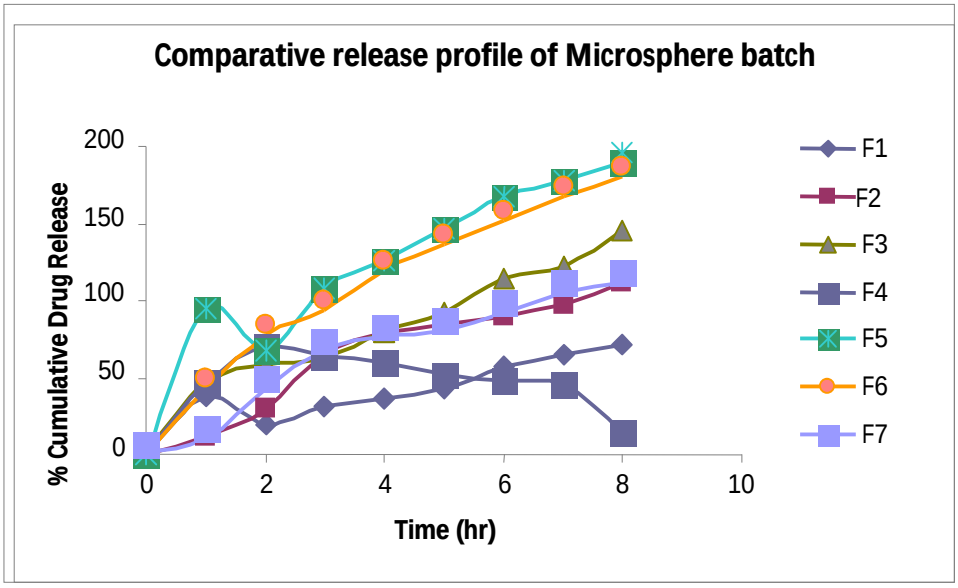

Fig1- Comparative release profile of Microsphere batch

3. RESULTS AND DISCUSSION

The results of FTIR spectral showed that there was no significant interaction between the drug and polymer. This was confirmed by the characteristic peaks of pure drug MTH in FTIR spectra (Fig.2-3).

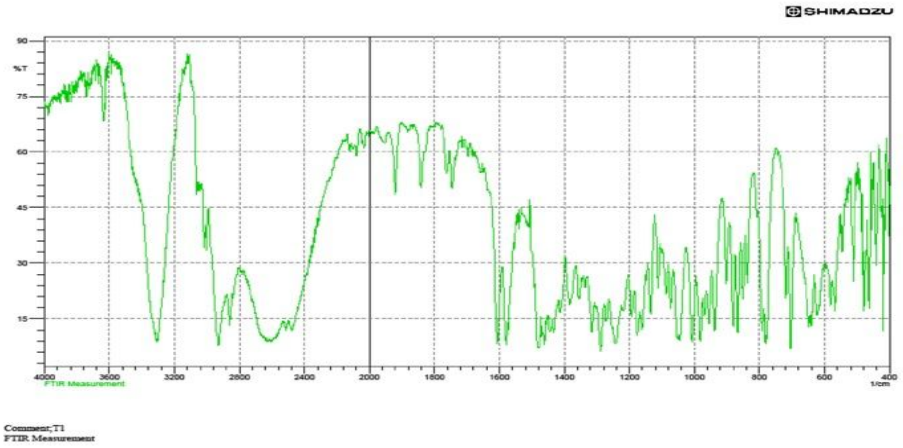

Fig2-FTIR spectra of drug Metformin Hydrochloride

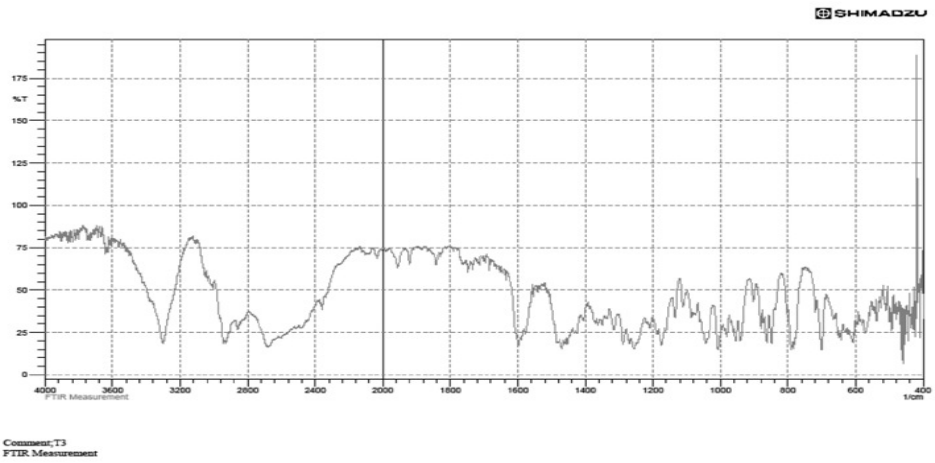

Fig3-FTIR spectra of physical mixture of Metformin Hydrochloride and albumin

The results of % yield of albumin microspheres were 85.16% to maximum of 98.87%. The maximum yield was obtained with formulation F5. On further analysis of drug encapsulation

of albumin microspheres, the encapsulation efficiency was found to be between 38.35-60.75%. Results are shown in table2. As the polymer concentration increases the drug encapsulation was found to be increasing in albumin microspheres. So based on this study, the drug release profile of all the formulations were carried out in Phosphate buffer pH 7.4.

Table2: Data for % yield & Drug encapsulation efficiency of MTH albumin microspheres

Formula Code	Percentage yield (%)	Drug encapsulation efficiency (%)
F1	89.48	38.35
F2	92.86	41.89
F3	88.52	53.60
F4	93.31	60.75
F5	98.87	64.71
F6	85.14	67.50
F7	88.14	69.85

Table 3: Data for In-vitro drug release profile of MTH Albumin microspheres

Time in (Min)	Cumulative % Drug Release						
	F1	F2	F3	F4	F5	F6	F7
30	12.32	27.41	39.91	37.86	39.68	19.18	48.62
60	13.73	32.36	45.59	44.00	45.36	21.96	66.62
90	24.77	37.32	48.59	47.64	48.32	31.68	87.45
120	27.36	39.82	51.55	54.05	56.09	40.05	99.51
150	32.26	41.41	56.68	64.16	65.27	44.32	91.88
180	38.59	45.73	59.05	68.27	73.81	50.73	81.42
240	41.55	47.23	63.00	75.50	81.03	59.82	72.36
300	50.00	55.73	69.23	80.00	82.84	69.73	56.39
6 hr	53.05	58.82	75.14	84.53	88.73	75.55	48.62
7 hr	61.55	68.59	85.18	89.07	93.31	80.05	66.62
8hr	74.68	88.14	89.73	91.59	98.87	85.90	87.45

The dissolution studies revealed that albumin microspheres released the drug completely up to 8 hours and out of different batches F5 was found to have better drug release profile than other formulations.

Table 4: Regression co-efficient and rate constants for release of Microsphere Batch F5

Microsphere batch	Zero order		First order		Higuchi matrix	
	r	**k_0**	**r**	**k_1**	**r**	**k_H**
F5	0.974	3.295	0.757	3.296	0.998	5.435

The data for In-vitro drug release profile of MTH albumin microspheres is shown in table- 3 and the comparative release profile of these formulations was shown in figure-3. The particle size was of the microspheres was found to be 99.6 μm and the size of the microspheres was found to increase with increased polymer loads which may be due to increase in viscosity of polymer solutions at higher concentration.

4. CONCLUSION

An emulsion solvent evaporation technique has been successfully employed to produce MTH loaded egg albumin microspheres with maximum drug encapsulation and desirable release profile. The formulation variable drug-polymer ratio exerted a significant influence on the drug encapsulation. Formulation of microspheres F5 (MTH: Albumin;1:3) was found the best among all. The present study signifies the utility of microspheres in retarding the drug release. This may in turn reduces the frequency of dosing, thereby improving the patient compliance.

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