Educational Administration: Theory and Practice
2024, 30(6), 3276-3282
ISSN: 2148-2403
https://kuey.net/

Research Article

Formulation And Characterization Of Combination Drug Microspheres For Diabetes Mellitus Management

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Citation: Muskan Bhagat, et al (2024), Formulation And Characterization Of Combination Drug Microspheres For Diabetes Mellitus Management, *Educational Administration: Theory and Practice*, 30(6), 3276-3282, Doi: 10.53555/kuey.v30i6.5209

ARTICLE INFO **ABSTRACT**

The current study aims to minimize dose frequency, dose amount and enhance patient compliance by designing and thoroughly analysing microspheres prepared with combined drugs that is metformin hydrochloride and saxagliptin, an antidiabetic medication which can enhance therapeutic effectiveness in combination therapy. The microsphere was developed using the solvent evaporation approach with metformin and saxagliptin as a main drug and polymers used are sodium alginate to enhance permeability along with guar gum and ethyl cellulose as the coating polymer. The microspheres were evaluated for percentage yield, particle size, drug entrapment efficiency and drug content, morphology, and in vitro drug release study. Fourier-transform infrared spectroscopy was used to examine the drug-polymer interaction; the results showed no incompatibility. The range of the drug entrapment efficiency was 60.63-95.51%. The produced microspheres of batch F6 had demonstrated, among other formulations, the ideal percent drug encapsulation of microspheres and the slow release of the drugs for roughly 14 hours. From this study, it is concluded that the developed polymeric microspheres of metformin hydrochloride and saxagliptin can be helpful for the management of diabetes mellitus by prolonged release of drugs, reduced dose frequency and dose interval and also by increasing patient compliances.

Keywords: Metformin, saxagliptin, sodium alginate, ethyl cellulose, solvent evaporation, encapsulation

INTRODUCTION:

Diabetes mellitus is a macromolecule metabolism condition that affects the body's capacity to regulate blood sugar levels through endocrine responses. (Saha et al., 2020) It is a complex condition that causes numerous complications globally. It is considered one among the top five causes of death globally. Diabetes affects around 150 million people worldwide. (Chatterjee *et al.*, 2018)

One of the most effective ways to administer drugs is orally. (Krishnakanth *et al.*, 2015) It's limited absorption through a certain stretch of intestinal limits and short circulation half-life are its two main characteristics. (Kadam N. R. and Suvarna V., 2015) Because of this pharmacokinetic defect, multiple dosages of drug are required to achieve therapeutic effect. Enhancing the pharmacokinetic and pharmacodynamic characteristics results in heightened bioavailability. When the drug therapy achieves the target concentration in blood or tissue, it is said to be effective. Goal is achieved because of the dosing scheme's good nature. (Patel *et. al.*, 2020)

A microsphere is a structure made up of a continuous phase of one or more miscible polymers that distributes macro- or molecular-level drug particles. On the other hand, they could be described as a single, solid ball or medicinal substance that is dispersed as a molecular dispersion of particles throughout the matrix. Microspheres are small spherical particles that usually have a diameter between 1 and 1000µm. Microspheres are sometimes referred to as microparticles. (Ingle *et al.*, 2023)

The drug must be administered to the target tissue in the appropriate amount and at the proper time with the least degree of toxicity and side effects in order to have the best possible therapeutic efficacy. When using prolonged controlled release techniques, there are various ways to get a medication to the right place. The use of microspheres as medication carriers is one method for doing this. The creation of novel controlled release

drug delivery systems is one of the most exciting fields of pharmaceutical science research. A well-designed controlled drug delivery system can boost the therapeutic efficacy of a particular medication and eliminate some of the issues with conventional therapy. (B. Sree Giri Prasad *et al.*, 2014)
Metformin, a white crystalline powder containing a 1,1- dimethyl biguanide analog, has been used as an anti-diabetic drug since ancient time. The chemical name is N-N-dimethyl imido di-carbon amide diamide hydrochloride. As a member of the biguanide family of antidiabetic active ingredients, metformin hydrochloride is used to treat type II diabetes. It works by increasing the activity of insulin and inhibiting gluconeogenesis to control blood sugar levels. (Hichem Tahraoui *et al.*, 2023) Saxagliptin is an antidiabetic drug prescribed to treat type 2 diabetes. It works by blocking dipeptidyl peptidase-4 (DPP-4). DPP-4 inhibitor are medications that disrupt the body's normal synthesis of incretins, which are hormones. Incretins reduce blood sugar levels by increasing the body's sugar consumption, primarily through enhanced pancreatic insulin synthesis, and decreasing the liver's sugar production. (Madhurilatha *et al.*, 2017) In individuals with type 2 diabetes, saxagliptin reduced mean HbA1c levels (compared to a placebo) over the course of a 24-week experiment. (Dhillon S, Weber J, 2009) Combination therapy of metformin and saxagliptin proved to be more successful than either drug used alone.
In present work, a polymeric microsphere was developed for the combination of metformin and saxagliptin by solvent evaporation method using afore mentioned polymers. The microencapsulation process is based on the solvent evaporation method, which combines the polymers of guar gum, ethyl cellulose, and sodium alginate.

MATERIALS AND METHOD:

Metformin Hydrochloride was procured from the Airmid Chemicals Pvt Ltd, Mumbai, India. Saxagliptin, sodium alginate, ethyl cellulose, guar gum, liquid paraffin, and ethanol was provided by Dev Bhoomi Uttarakhand University, Dehradun, Uttarakhand. Analytical grade solvents and chemicals were all used in the formulation.

Microspheres preparation:

A non-aqueous solvent evaporation approach was used to create microspheres using metformin hydrochloride and saxagliptin as core materials. The drugs and polymers were combined in ethanol at different ratios. At the room temperature, the slurry was mixed with 30 ml liquid paraffin and agitated at a 1200 rpm using a magnetic stirrer. The solution was agitated for 4 hours to allow the solvent to drain, and the microspheres were recovered by filtering using Whatman filter paper no. 1. The microspheres were repeatedly clean with petroleum ether (40-60^{o}C) until they were oil-free. The microspheres were collected, dried for three hours at room temperature, and stored in a desiccator containing fused calcium chloride. (Durgapal *et al.*, 2017)

Table No. 1 Formulation composition of prepared microspheres using sodium alginate alone and in combination with ethyl cellulose and guar gum

S. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Metformin(mg)	100	100	100	100	100	100	100	100	100
2	Saxagliptin(mg)	5	5	5	5	5	5	5	5	5
3	Sodium Alginate(mg)	200	300	400	200	300	400	200	300	400
4	Ethyl cellulose(mg)	-	-	-	100	100	100	-	-	-
5	Guar Gum(mg)	-	-	-	-	-	-	100	100	100
6	Ethanol(ml)	12	12	12	12	12	12	12	12	12

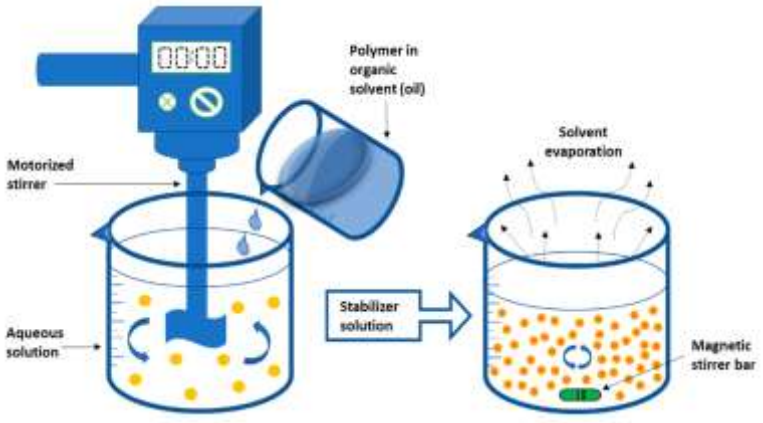

Figure 1. Polymeric microspheres preparation

Evaluation of prepared microspheres:

Percentage yield determination:

1. Accurate weight measurements were taken for dried microspheres.

2. The percentage yield was then computed using formula shown below. (Kesharvani *et al*., 2020)

$$\text{Percentage yield} = \frac{\text{Weight of obtained microspheres}}{\text{Total weight of drug and polymer}} \times 100$$

Particle size determination of microspheres:

The particle size of each batch of microspheres was measured using an optical microscope calibrated with a stage micrometre.

Drug content determination in microspheres:

- The 50 mg microspheres were dissolved in ethanol and diluted with 50 ml of 0.1N hydrochloric acid in a 100 ml of volumetric flask.
- The liquid was agitated until the formulation was destroyed. The solution went through Whatman filter paper.
- After diluting with ethanol, the UV-VIS spectrophotometer was used on a Shimadzu UV-1800 at 222.6 nm

$$\text{Loading drug content} = \frac{\text{Weight of drug in the microsphere}}{\text{Total weight of microsphere}} \times 100$$

Drug entrapment determination in microspheres:

Drug entrapment in microspheres was determined by the equation given below:

$$\text{Entrapment Efficiency} = \frac{\text{Practical Drug Content}}{\text{Theoretical drug content}} \times 100$$

Micromeritic properties of prepared microspheres:

Prepared microspheres were evaluated for the micromeritic properties such as angle of repose, bulk density, tapped density and compressibility index.

Angle of repose:

Using a fixed-position funnel, the greatest angle between the surface of the microsphere pile and the horizontal plane was determined in order to verify the angle of repose.

$$\theta = \tan^{-1}(h/r)$$

Bulk density:

A graduated cylinder was filled with the pre-weight (M) blend in order to determine the apparent bulk density. The blend's bulk volume (V_o) was computed. The formula was used to estimate the bulk density.

$$\text{Bulk density} = \frac{M}{V_o}$$

Tapped density:

The lowest volume (V_t) occupied was measured after tapping a measuring cylinder containing a known mass (M) of the mix for a predetermined amount of time. The following formula was used to estimate the tapped density.

$$\text{Tapped density} = \frac{M}{V_t}$$

Compressibility index:

Microsphere`s tendency to be compressed is known as compressibility index. It is calculated by the formula given below.

$$\text{Compressibility index} = \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}} \times 100$$

Morphological characterization:

- SEM was used to evaluate the shape and size of the microspheres loaded with metformin hydrochloride and saxagliptin.
- The samples were mounted on a metal stub using adhesive tape on both sides.
- Carbon coating was applied in a high vacuum evaporator.
- The procedure of scanning and taking photographs was completed.

In vitro drug release study:

For metformin hydrochloride:

- In vitro drug release investigations were carried out using a USP dissolving Test Apparatus Type 1 (Basket Type) at 37°C and 100 rpm in 900 ml of dissolving media.
- The study employed 100 mg of produced microspheres that were correctly weighed.
- The test used 0.1N HCl as a dissolving medium.
- 5 ml of the sample were taken out of the dissolution media and replaced with 5 ml of fresh medium at intervals of 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, and 24 hours.
- The sample was analysed using a UV-Visible spectrophotometer at 233 nm after passing through W.F.P.

For saxagliptin:

- In vitro release tests were performed in a 0.1N HCl medium. Microspheres carrying 50 mg of drug in capsules were dropped into vessels holding 900 ml of 0.1N HCl medium at 37°C. (Farheen *et al.*, 2018)
- The USP dissolving test apparatus type 1 (basket type) was set to 50 rpm for 12 hours.
- At one-hour intervals, 5 ml of samples were removed from dissolution media.
- To preserve the sink state, the dissolution vessel was filled with an equivalent volume of medium at the same temperature.
- The absorbance of the filtrate at 210 nm was measured, and the percentage of drug release was estimated.

RESULTS AND DISCUSSIONS:

Polymeric microspheres of metformin hydrochloride and saxagliptin were created using sodium alginate, ethyl cellulose and guar gum, either sodium alginate alone or in combination with various drug and polymer ratios (see table 1). Solvent evaporation method was used to achieve the desired results. Formulations F1–F3 were made with increasing concentrations of sodium alginate, while F4–F6 were made using sodium alginate and ethyl cellulose at various ratios and a fixed drug concentration of 100 mg and 5mg respectively. Polymers like sodium alginate and guar gum were combined in F7-F9 formulations. The formulations kept the drugs amount constant while altering the amount of both polymers relative to each other.

Percentage yield and Particle Size:

The percentage yield of solvent evaporation method formulations (table 2) ranged from 67-78%, indicating a high yield. The testing results showed a clear correlation between polymeric concentration and yield percentage. In most situations, increasing polymer concentration led to higher yield percentages.

The solvent evaporation method approach produced spherical, discrete microspheres. Table 2 shows optical microscopic data for each formulation. The microspheres ranged in size from 100-300 µm and increased with polymer content.

Table no. 2 % yield, particle size, drug content and drug entrapment parameters of microsphere formulations F1 to F9

Batch no.	% yield	Particle size(µm)	% drug loading	%DDE
F1	69.7±2.91	160.1±1.71	10.30±0.45	79.94±1.23
F2	67.5±3.95	177.5±3.17	14.68±0.75	83.99±1.03
F3	73.6±2.87	199.7±1.92	11.01±0.54	87.79±1.29
F4	76±1.30	175.1±2.34	13.13±0.74	60.63±1.56
F5	74.6±1.67	196.3±1.23	15.70±0.59	68.75±0.07
F6	78.1±2.17	231.9±2.19	17.41±0.53	95.51±0.94
F7	68.2±1.79	168.8±3.65	12.08±0.49	65.03±1.79
F8	73±1.17	200.5±3.15	16.91±0.08	70.67±0.09
F9	71.7±1.05	214.9±1.56	15.09±0.01	85.41±1.92

Drug loading and drug entrapment efficiency:

The formulation's drug loading and entrapment efficiency ranged between 10.30-17.41% and 60.63-95.51%, respectively. Formulation F6 had the highest drug loading (17.41%) and entrapment efficiency (95.51%) among the nine drug-loaded formulations tested (F1-9). The %EE is found to be increased with the increase in drug/polymer ratio. (G.Pandey *et al.*, 2016) Table 2 displays the findings of determining drug loading and entrapment efficacy in formulations.

Micromeritic properties:

All micrometric parameters were within acceptable ranges.

Table No 3 indicates that all formed microspheres have reasonable flow properties, with angles of repose ranging from 21 to 29°.

All formulations' bulk and tapped densities fell between 0.66 and 0.80 gm/cm3 and 0.71 and 0.95 gm/cm3, respectively.

Formulations (F1, F3, F4, F5, F6, F8) with compressibility indexes ranging from 5.78 to 20.00% had outstanding flow-ability, while formulation (F2, F7, F9) had fair flow-ability.

Table no. 3 Micromeritic properties of microsphere formulation F1 to F9

Batch no.	Angle of repose	Bulk density	Tapped density	Compressibility index
F1	24.67	0.75±0.04	0.84±0.01	12.87
F2	27.07	0.66±0.01	0.86±0.01	19.91
F3	21.59	0.76±0.02	0.95±0.02	5.78
F4	25.12	0.71±0.03	0.71±0.07	10.35
F5	24.57	0.80±0.01	0.81±0.05	13.10
F6	26.78	0.77±0.05	0.72±0.03	9.45
F7	30.38	0.72±0.06	0.76±0.02	20.00
F8	28.39	0.73±0.01	0.86±0.04	11.64
F9	25.91	0.76±0.02	0.78±0.07	18.07

Optimization of formulation:

Formulation F6 outperformed other formulations in terms of % yield (78.1%), drug loading (17.41%), and entrapment efficiency (95.51%). The optimized formulation (F6) was subjected to further tests, including SEM, FTIR and drug release, based on the parameters listed above.

Figure 2. Prepared microspheres (F6)

SEM (Scanning electron microscopy):

SEM analysis of best formulation batch F6 from different angles reveals distinct metformin hydrochloride and saxagliptin loaded microparticles with a rough outer surface and corrugations.

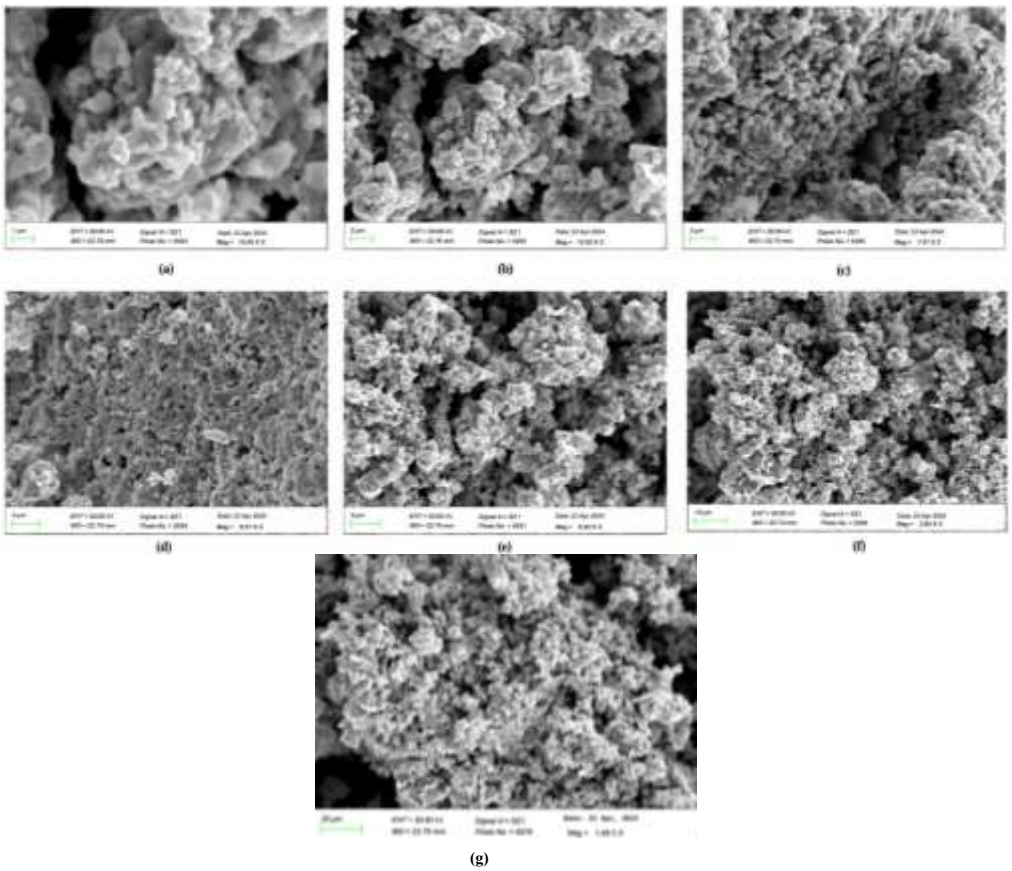

Figure 3. SEM analysis of metformin hydrochloride and saxagliptin loaded microspheres of formulation F6 from different angle (a) at 1µm (b) at 2µm (c) at 3µm (d) at 4µm (e) at 5µm (f) at 10µm (g) at 20µm

Compatibility study:

FTIR: The pure drug's compatibility with the other excipients in the formulation was assessed using FT-IR spectra. The drugs distinctive peak did not alter with the polymer utilized in the microsphere formulation, indicating no interaction between the two. Peaks appear at the expected range verifies that the materials used in the study are genuine.

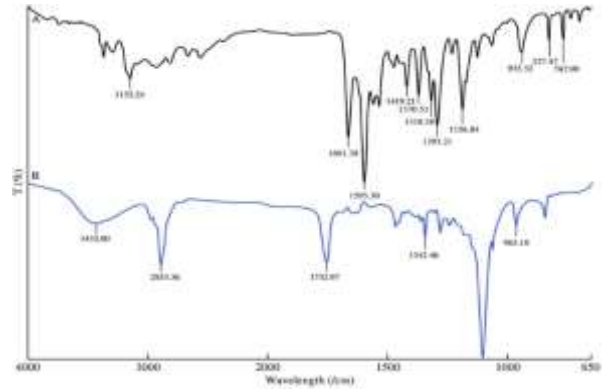

Figure 4. FTIR of metformin and saxagliptin

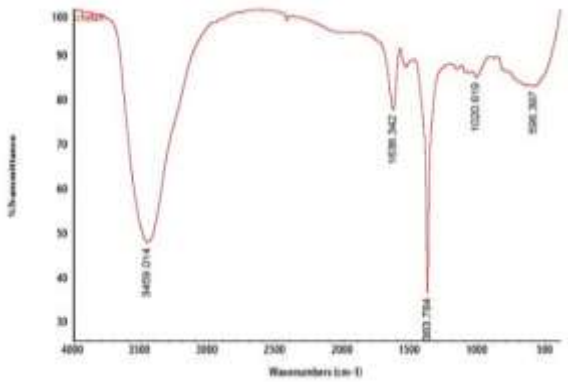

Figure 5. FTIR of formulation F6

In vitro drug release study:

The in vitro drug release study, revealed that the metformin and saxagliptin loaded microsphere optimized formulation (F6) exhibited prolong, controlled and slow release (i.e. 68.38% for metformin and 67.56% for saxagliptin) 0.1N HCl up to 14 hours. The formulation F4-F6 were prepared using sodium alginate and ethyl cellulose in which F6 shows slow and controlled release due to polymer concentration and formation of polymeric matrix. The USP Dissolution Test Apparatus Type 1 (Basket Type) was used to conduct the in vitro analysis of the improved formulations (F6) in 0.1N HCl. The improved formulation (F6) demonstrated a prolonged period of regulated drug release, indicating that it functioned as a highly bioavailable drug delivery system with a controlled release profile.

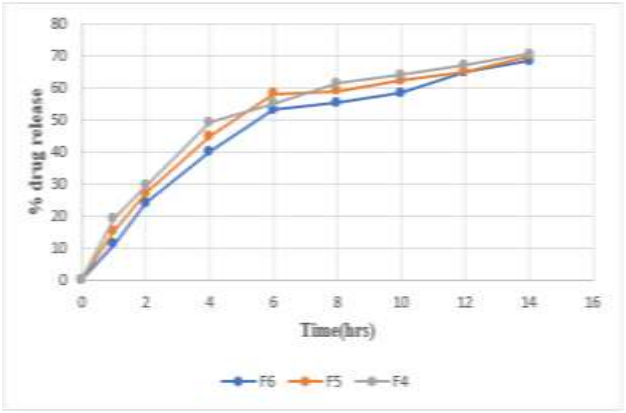

Figure 6. In vitro % drug release of Metformin Hydrochloride from F4 to

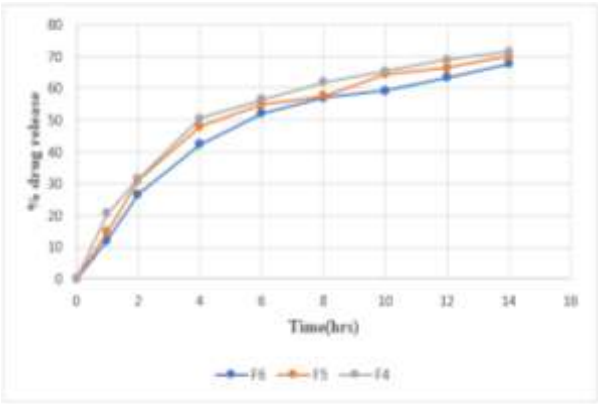

Figure 7. In vitro % drug release of Saxagliptin from F4 to F6

Conclusion:

Based on the above outcome, it was concluded that natural polymeric microspheres of metformin hydrochloride and saxagliptin were successfully developed using polymers such as sodium alginate, ethyl cellulose and guar gum at various ratios by Solvent evaporation method. For the purpose of managing diabetic mellitus, the polymeric microspheres containing a combination of saxagliptin and metformin hydrochloride were effectively created, optimized, and assessed. The microspheres were spherical in shape, with the drug distributed in the polymer matrix in an amorphous state. The microspheres were characterized using scanning electron microscopy (SEM), FTIR, and in vitro dissolving experiments. The FTIR spectrum of optimized batch F6 revealed no chemical interactions, indicating drugs compatibility with polymers. The formulation batch F6 was demonstrated optimal in vitro release and drug entrapment efficiency. The microspheres of F6 with in vitro drug release of 68.34% in 14 hours shows slow and controlled release of drug and maintain drug levels for extended period, this reduces side effects and dose frequency, resulting in improved patient compliance.

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