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Research Article

FORMULATION AND EVALUATION OF METFORMIN HYDROCHLORIDE LOADED MUCOADHESIVE MICROSPHERES

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ABSTRACT

Metformin Hcl is a biguanide antidiabetic agent which is used in the management of type 2 diabetes and it is preferably absorbed in the upper part of the GIT and readily soluble in gastric pH of the stomach. The present study, Metformin Hcl was formulated to develop gastro retentive formulation using sodium alginate and different concentration of natural mucoadhesive polymers such as xanthan gum and guar gum by ionic gelation technique with an aim to controlled release and improve bioavailability. Six formulations were prepared by using different drug to polymer ratios, were evaluated for relevant parameters. Depending upon the drug to polymer ratios, the percentage yield is found between 78.06±0.51% to 89.35±0.83% in all formulations. The entrapment efficiency of prepared microspheres was in the range of 83.60±0.71% to 97.16±0.53%. Microspheres showed a good specificity, spherical in shape and the mean particle size of microspheres significantly increase with increasing polymer concentration and it was in the range between 22.42±0.12µm to 30.12±0.41µm. Swelling Index of the mucoadhesive microspheres was in the range of 66.37± 0.07% to 55.07± 0.05%. *In-vitro* drug release studies was performed in simulated gastric fluid, it is revealed that formulation code XG-III was 94.96±0.16% and GG-III was 92.98±0.22% drug releases at the end of dissolution studies respectively, when compared to all batches due to increases in polymer concentration. Stability studies of selected Metformin Hcl mucoadhesive microspheres showed good results. It could be also concluding that the all the formulations were shown satisfactory results and suitable for potential therapeutic uses.

Keywords: Metformin Hcl, Mucoadhesive Microspheres, Sodium Alginate, Xanthan Gum.

INTRODUCTION

An oral controlled release dosage form is associated with several physiological difficulties such as inability to locate within the desired region of the GIT due to brief gastric emptying time. This normally averages of 2-3 hrs through the major absorption zone, mainly stomach and intestine, results in incomplete drug release leading to reduced efficacy of the administered dose. So designing a controlled release system is to deliver the drug at a rate necessary to achieve and maintain a constant drug blood level.[1]

Microspheres based novel drug delivery system may increase the life span of active agents and have considerable attention in controlled release and target drug to a specific body site of interested area without side effects, and it's limited owing to their short residence time at absorption site. So, various attempt have been made to increase the bioavailability as well as prolong the gastric residence time in the stomach resulted in development of bioadhesive drug delivery system (BDDS) which will provide an intimate contact with the absorbing membranes. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach which enhance drug absorption. This can be achieved

by coupling mucoadhesion characteristics to microspheres. Developing mucoadhesive microspheres bind to the mucus layer covering the mucosal epithelial surface and increases the residence time of the formulation at the place of absorption/delivery site and have efficient absorption, enhanced bioavailability of drugs and specific targeting of drug to the absorption site using lower drug concentration.[2]

Diabetes (Diabetes mellitus) is a metabolism disorder has a condition in which the quantity of glucose in the blood is too elevated and it's characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, and it may present with characteristic symptoms such as thirst, polyuria, blurring of vision, weight loss, risk of cardiovascular, peripheral vascular and cerebrovascular disease etc., which is controlled by using anti-diabetic drugs. Metformin Hcl is a biguanide class antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, which decreases blood glucose levels by decreasing hepatic glucose production, decreases intestinal absorption of glucose and improving insulin sensitivity by increasing peripheral glucose uptake and utilization. It is a short biological half-life of 3.4 ± 0.7 hours and the absolute bioavailability under fasting conditions is approximately 50-60%. Studies of single oral doses indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. So most anti-diabetic drug, are having short half life and low bioavailability require frequent administration causing fluctuations of drug in plasma.

The present work is to formulate an oral controlled release dosage form for anti-diabetic drug using Metformin Hcl, as they release drug slowly with prolonged gastric retention in GIT and maintain constant drug levels in plasma for extended period.[3] It is necessary to develop microspheres preparation from naturally occurring mucoadhesive polymers, which adhere to the mucosa and release the drug in slow and controlled manner and there by maintaining blood glucose levels. This study is an attempt to prepare mucoadhesive microspheres loaded Metformin Hcl using different natural gums with varying ratios and evaluate the microspheres characterization.[4]

MATERIALS AND METHODS

MATERIALS

Metformin Hydrochloride was obtained as a gift sample from Yarrow Chem Products, Mumbai, India, Sodium Alginate from Qualigens Fine Chem Pvt Ltd, Mumbai, India, Calcium Chloride and Guar gum from Balaji drugs Pvt Ltd, Mumbai, India, Xanthan gum from Yarrow Chem Products, Mumbai, India.

METHODS

IR Spectral Analysis

The FT-IR spectrum of metformin hydrochloride and polymers was recorded using KBr mixing method on the FT-IR instrument (Schimadzu FTIR instrument). The drug alone, and in combination with polymers (mixed in the ratio of 1:1) was taken and subjected to FT-IR studies.[5]

Preparation of Mucoadhesive Microspheres of Metformin Hcl

Mucoadhesive Microspheres were prepared by using different ratios of Metformin Hcl, sodium alginate, guar gum and xanthan gum. Sodium alginate was dissolved in deionized water to form a homogeneous solution (2% w/v). Guar gum and xanthan gum were dissolved separately with deionized water to get viscous and sticky solutions. The pure drug was dispersed in the solution of gum and then sodium alginate solution was added to it with vigorous stirring until formation of an even dispersion. The resulting dispersion was then extruded drop wise into the 100 ml calcium chloride solution (10% w/v) through a 23G syringe. The formed beads were retained in the calcium chloride solution for 15 minutes to complete the formation of spherical rigid microspheres. They were collected by decantation, washed and dried at room temperature and subsequently stored in desiccators. Same procedures were repeated for all batches of formulation.[6] In this study, six formulations were prepared by different ratios of drug and polymer as given in Table 1 and were evaluated for relevant parameters.

Characterization of Mucoadhesive Microspheres

Percentage Yield

The prepared microspheres were collected, dried at room temperature and then weighed. The measured weight of prepared microspheres was divided by the total amount of all excipients and drug used in the preparation of microspheres which will give the total percentage yield of microspheres.[7]

$$\text{Percentage yield (\%)} = \frac{\text{Amount of microspheres obtained (gm)}}{\text{Theoretical amount (gm)}} \times 100$$

Determination of particle size

The sample of prepared microspheres was randomly selected and their size was determined using an optical microscopy (Olympus, India) method.[8]

Micromeritic Properties

The Mucoadhesive microspheres were characterized by their Micromeritic properties such as bulk density, tapped density, carr's index, hausner's ratio and angle of repose. [9-10]

Morphological Studies

The surface morphology of Metformin Hcl mucoadhesive microspheres were determined by Scanning Electron Microscopy (JEOL, JSM-6701 F, JAPAN) operating at 15 KV. [11-12]

Entrapment Efficiency

The amount of drug entrapped was estimated by crushing the calculated quantity of microspheres and extracting with aliquots of 0.1N Hcl (pH 1.2) and it was transferred to a 100 ml volumetric flask and the volume was made up by using same medium. The solution was filtered and the absorbance was measured by spectrophotometer against appropriate blank. The amount of drug entrapped in the mucoadhesive microspheres was calculated by the following equation. [13-14]

$$\text{Entrapment efficiency (\%)} = \frac{\text{Estimated percent drug content}}{\text{Theoretical percent drug content}} \times 100$$

In-vitro Drug Release Studies

The *in-vitro* drug release studies were conducted in gastric pH using paddle type dissolution apparatus under sink conditions. Accurately weighed samples of the microspheres was introduced in to 900 ml of dissolution medium (pH 1.2) maintained at 37±0.5^0 C with paddle rotating at 100 rpm. Aliquots samples were withdrawn every 1 hr and the same volume of fresh medium was refilled for the maintains of sink condition. After suitable dilution the samples are analyzed spectrophotometrically at 233 nm [15-16]. And in order to study the exact mechanism of drug release, *in-vitro* release data was analyzed using different kinetics models and mechanism of drug release is determined.[17-18]

Swelling Studies

The calculated quantity of dried microspheres from each batch was placed in dissolution solution for at least 10 hrs. The wet weight of the swollen microspheres was determined by first blotting the microspheres with filter paper to remove surface water and then weighing them immediately. The percentage (%) swelling of microspheres was calculated using following formula:

$$S = (We - Wo) / Wo \times 100\ \%$$

We = weight of the gel microspheres at equilibrium swelling; Wo = initial weight of the microspheres.[19]

Stability Studies

Best formulations were placed in borosilicate screw capped glass containers and stored at different temperatures (27±2^{0}C, 60± 5% RH & 40±2^{0}C, 70± 5% RH) using stability chamber. At the end of specified day's period, the samples was withdrawn and analyzed for their drug content.[20]

RESULTS AND DISCUSSION

IR spectral analysis

FT-IR spectra were taken in the wavelength region of 600-3800 cm^{-1} at ambient temperature and the resolution was 4 cm^{-1} and compared the position and relative intensity of absorption band of physical admixtures and pure drug is illustrated in Figure 2 to 3. In compatibility studies, IR spectrum of pure drug was found to be similar to the standard IR spectrum of which indicates that the obtained sample was pure Metformin Hcl. The IR spectra of all the pure samples and the Metformin Hcl physical admixtures of suitable proportion of polymers were subjected to the study and from the results, It has been observed that there is no chemical interaction between drug and the polymers used, also there was no considerable changes in comparison between the ratios of percent (%) transmittance.

Percentage yield, Particle size and Drug entrapment

From Table-2, Percentage yield of all formulations is between the ranges of 78.06% to 89.35%. From the results it was observed that, the concentration of polymer increased, the percentage yield of the mucoadhesive microspheres was also slightly increased. The mean particle size of microspheres significantly increases with increasing polymer concentration and it was in the range between 22.42±0.12µm to 30.12±0.41µm. A high concentration of polymer produced a more viscous dispersion, which formed larger droplets and consequently larger microspheres. The particle size of 1:0.75 ratio microspheres are more than that of 1:0.25 microspheres. The

percentage Entrapment efficiency of all formulations is found in the ranges of 83.60±0.71% to 97.16±0.53%. It was observed that the entrapment efficiency of microspheres is increase with increasing the polymer concentration. A maximum of 97.16% of drug entrapped in Metformin mucoadhesive microspheres which were prepared by xanthan gum (1: 0.75) batches.

Micromeritic properties

From Table-3, it was observed that bulk and tapped density values were lies in between 0.543 to 0.636 and 0.577 to 0.733 g/cm^3 respectively. The carr's index values were lies between 5.82% to 12.32% indicates excellent flow characteristics of the microsphere and Hausner's ratio were lies between 0.869 to 0.949 using different formulations. Angle of repose of all formulated microspheres is found to be less than 40° indicates acceptable flow properties.

Morphological studies

The surface morphology of best formulations (XG-III & GG-III) was determined by scanning electron microscopy (SEM) for characterization of microspheres. Photomicrograph 1&2 results showed that the prepared microspheres showed a good specificity, spherical and uniform in shape with smooth surface. And the surface smoothness of prepared microspheres was decreased by increasing the polymer concentration is confirmed by SEM.

Swelling index (SI)

From the results of Table-4, formulation GG-I showed least percentage swelling of 43.29±0.08%, while XG-III showed highest swelling of 66.37±0.07% at least 10 hours attributed to the relative density of microspheres in higher polymer concentrations. The fundamentals that the increase in degree of swelling depends on polymer concentration in formulation and it may be attributed to the pores and cavities present in them. It was observed that the xanthan gum formulations (XG-I to XG-III) showed greater percentage and good degree of swelling index than guar gum batches.

***In-vitro* drug release studies**

The release profile of all batches of microspheres using different ratios was studied in 0.1N Hcl (pH 1.2), for a period of 10 hours. The comparative *in-vitro* drug release curve of all batches of mucoadhesive microspheres was shown in Figure 4&5. From the results, it was observed that, the drug releases from the formulations XG-III and GG-III was found to be 94.96% and 92.98% at the end of dissolution studies which showed prolonged and controlled release of Metformin Hcl and its indicated that the amount of drug release decreases with increase in polymer concentration. The increased concentration of polymers leads to increased density of polymer matrix into the microspheres which results in increased diffusional path length.

The results obtained from *in-vitro* release studies were analyzed in various kinetic models of data treatment as follows: Cumulative percentage drug release Vs Time (Zero order rate kinetics), Cumulative % drug retained Vs Time (First order rate kinetics), Cumulative percentage drug released Vs Square root of Time (Higuchi's classical diffusion), Log cumulative percentage drug release Vs log Time (Korsmeyer-Peppa's exponential). The kinetics data results are shown in Table-5.

In order to understand the mechanism and kinetics of drug release studies of all formulations were subjected to goodness of fit test by linear regression analysis according to various kinetics models. From the results, the correlation coefficient (r) values of all formulations (XG-I to XG-III & GG-I to GG-III) followed zero order kinetics were found to be 0.9964, 0.9949, 0.9957, & 0.9910, 0.9953, 0.9912 respectively. So the co-efficient of determination indicated that the release data was best fitted with zero order kinetics (concentration was nearly independent of drug release). When the drug release data was put in to Higuchi's equation, good correlation coefficient (r) values 0.9779 to 0.9847 were obtained, indicating the drug release was diffusion controlled release mechanism. The release data obtained were also put in Korsmeyer-Peppas model in order to find out n values, which describe the drug release mechanism. Generally, on the basis of the diffusion exponent, an "n" value of 0.5 or less than 0.5 indicates the drug release mechanism approaches to a Fickian diffusion controlled release, where as "n" value from 0.5 to 1 indicates the drug release mechanism is Non-Fickian diffusion and the models with highest correlation coefficient (r) used for describing the mechanism of drug release.

From the kinetics result data, the n values of mucoadhesive microsphere were found in the range of 0.8105 to 0.8576 with correlation coefficient values ranging from 0.9508 to 0.9907, indicating Non-Fickian diffusion mechanism i.e., Non-Fickian of drug through metformin Hcl mucoadhesive microspheres. And the corresponding plot (log cumulative

percent drug release vs log time) for Korsmeyer–Peppas equation indicated a good linearity. Hence, the above observations, the release of drug from mucoadhesive microspheres provide a controlled release for a period of sufficient hours and the kinetics study shows that 'r' values of all formulated batches indicate compliance with Higuchi's plot and which reveals that the drug release follows Non-Fickian diffusion mechanism.[21]

Stability studies

From the *in-vitro* results, best formulations (XG-III) were taken and analyzed the stability studies. The results show that there is about 93.72% to 95.94% of drug present in the formulation with no-observable physical changes up to three months during storage. This indicates a good stability of the Metformin Hcl microspheres.

CONCLUSION

Metformin Hcl Mucoadhesive microspheres is obtained by using suitable ratio's polymer proportion of Xanthan gum and Guar gum and the formulated microspheres might be a better practical approach to achieve a prolonged therapeutic effect by continuously releasing the medication over extended period of time in the stomach. All formulations results were found to be satisfactory. Hence, it is concluded that mucoadhesive microspheres can be selected for the development of gastro retentive drug delivery system for potential therapeutic uses and these microspheres release the drug in the stomach and upper gastrointestinal tract and thereby improve the bioavailability.

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Table 1: Composition of Metformin Hcl Mucoadhesive microspheres

Formulations Code	Metformin Hcl (mg)	Sodium Alginate (%w/v)	Guar Gum (%w/v)	Xanthan gum (%w/v)	Calcium Chloride (%w/v)
GG1	100	2	0.25	-	10
GG2	100	2	0.5	-	10
GG3	100	2	0.75	-	10
XG1	100	2	-	0.25	10
XG2	100	2	-	0.5	10
XG3	100	2	-	0.75	10

Table 2: Percentage yield, Particle size and Drug entrapment of Mucoadhesive Microspheres of Metformin Hcl

Formulations Code	Percentage Yield (%)	Average Particle Size (µm)	Drug Entrapment (%)
XG-I	78.70 ± 0.67	24.31±0.22	86.64±0.34
XG-II	81.60 ± 0.90	26.52±0.43	89.56±0.93
XG-III	89.35 ± 0.83	30.12±0.41	97.16±0.53
GG -I	78.06 ± 0.51	22.42±0.12	83.60±0.71
GG-II	80.32 ± 0.58	25.12±0.04	88.19±0.74
GG-III	84.51 ± 0.12	27.92±0.53	93.96±0.41

Results are mean ± S.D of three trials (n=3)

Table 3: Micromeritic properties data of Metformin Hcl Mucoadhesive Microspheres

Formulations code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Hausner's ratio	Angle of repose (θ)
XG-I	0.543±0.003	0.577±0.003	5.82±0.42	0.949±0.23	$27^0.58'$±0.52
XG-II	0.617±0.007	0.683±0.003	9.54±0.25	0.913±0.42	$28^0.31'$±0..53
XG-III	0.625±0.002	0.697±0.002	9.89±0.56	0.901±0.34	$29^0.64'$±0.62
GG-I	0.557±0.004	0.609±0.005	7.54±0.43	0.924±0.21	$27^0.58'$±0.34
GG-II	0.638±0.005	0.732±0.004	11.24±0.13	0.881±0.54	$29^0.78'$±0.45
GG-III	0.636±0.004	0.733±0.002	12.32±0.82	0.869±0.21	$30^0.20'$±0..72

Results are mean ± S.D of three trials (n=3)

Table 4: Swelling index of Metformin Hcl mucoadhesive microspheres

Formulations code	Swelling index (%)
XG-I	52.19±0.02
XG-II	60.25±0.04
XG-III	66.37±0.07
GG-I	43.29±0.08
GG-II	49.05±0.03
GG-III	54.07±0.05

Results are mean ± S.D of three trials (n=3)

Table 5: Kinetic analysis data of Metformin Hcl mucoadhesive microspheres

Formulations Code	Release model							
	Zero order		First order		Higuchi's		Korsmeyer and peppa's	
	R	S	R	S	R	S	R	S
XG-I	0.9964	13.529	0.9751	-0.19	0.9843	34.47	0.9852	0.8256
XG-II	0.9949	12.598	0.9624	-0.14	0.9824	33.67	0.9890	0.8287
XG-III	0.9957	9.8207	0.9778	-0.10	0.9801	27.07	0.9763	0.8475
GG-I	0.9910	13.82	0.9788	-0.16	0.9832	33.60	0.9885	0.8309
GG-II	0.9953	11.99	0.9517	-0.13	0.9847	32.26	0.9907	0.8576
GG-III	0.9912	10.04	0.9702	-0.10	0.9779	28.44	0.9508	0.8105

Correlation coefficient (r), Slope(s)

Table 6: Stability studies data of Metformin Hcl mucoadhesive microspheres (XG-III)

At the end of period (in days)	Physical Appearance	Percentage Drug Content	
		At 27±2⁰C, 60± 5% RH	At 40±2⁰C, 70± 5% RH
30	No change	95.94±1.26	95.12±1.32
60	No change	95.08±1.45	94.86±1.46
90	No change	94.45±1.53	93.72±1.61

Results are mean ± S.D of three trials (n=3)

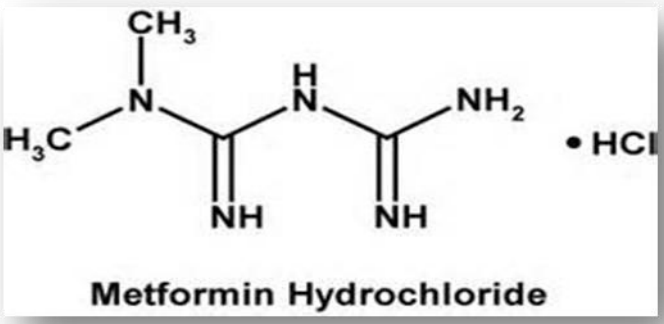


Fig. 1: Structure of Metformin Hydrochloride

Fig. 2: IR spectra studies of pure Metformin Hcl, Sodium Alginate, Xanthan gum and Physical Admixtures of Metformin Hcl, Sodium Alginate and Xanthan gum (MSX)

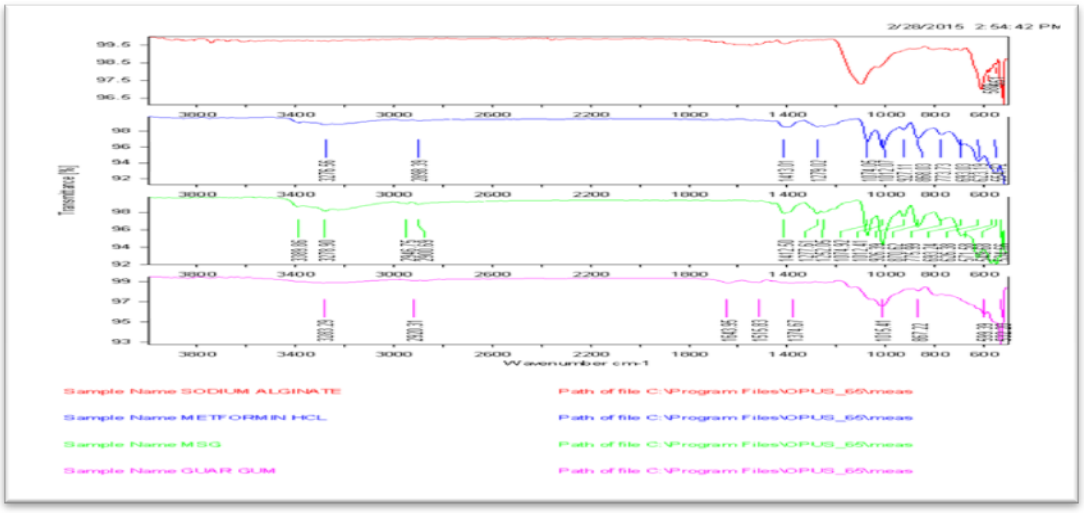


Fig. 3: IR spectra studies of pure Metformin Hcl, Sodium Alginate, Guar gum and Physical Admixtures of Metformin Hcl, Sodium Alginate and Guar gum (MSG)

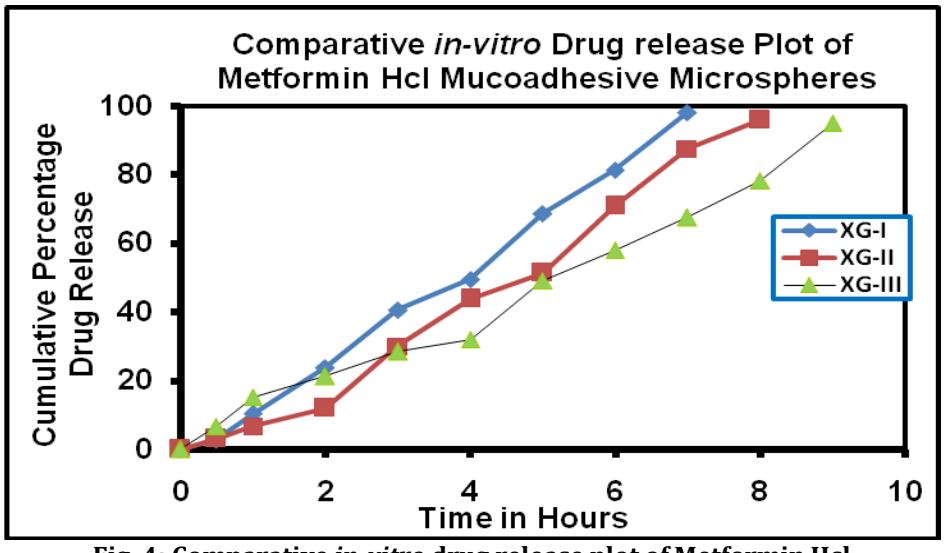


Fig. 4: Comparative *in-vitro* drug release plot of Metformin Hcl Mucoadhesive microspheres (XG-I to XG-III)

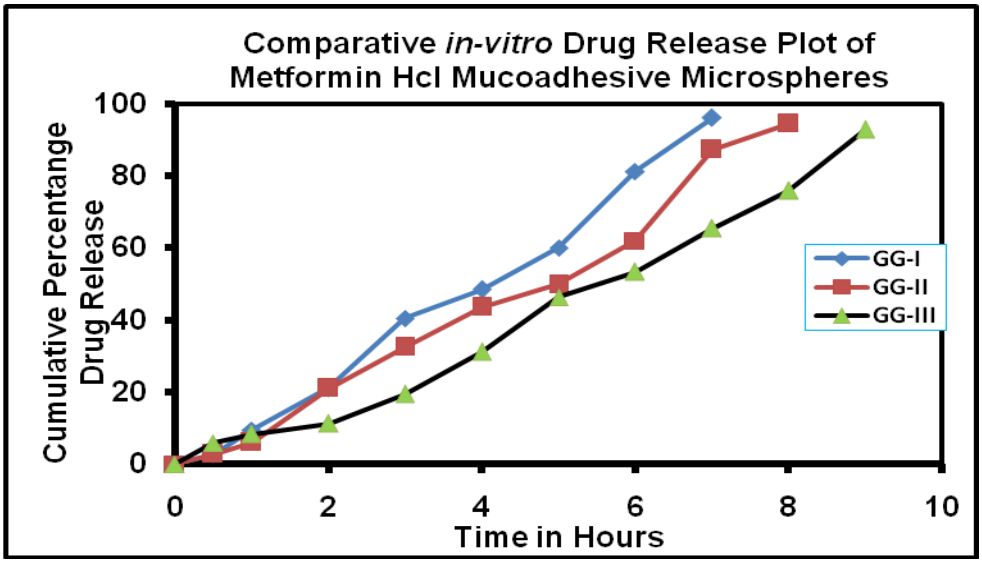
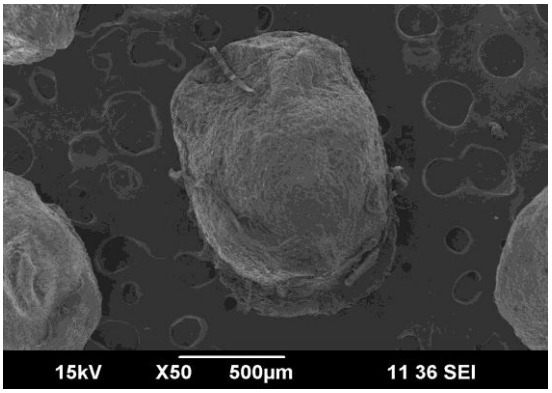
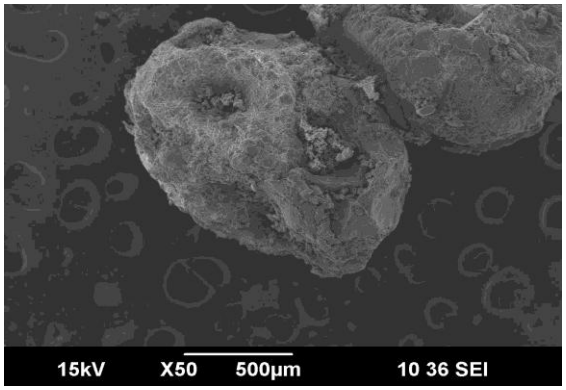


Fig. 5: Comparative *in-vitro* drug release plot of Metformin Hcl Mucoadhesive microspheres (GG-I to GG-III)



Photomicrograph-1
SEM image of Metformin Hcl Mucoadhesive microspheres (XG-III)



Photomicrograph-2
SEM image of Metformin Hcl Mucoadhesive microspheres (GG-III)

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