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Formulation and Evaluation of Sustained Release Mucoadhesive Microspheres of Metformin Hydrochloride

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ABSTRACT

Mucoadhesive microspheres of metformin hydrochloride (HCL) were successfully developed by emulsification /evaporation techniques to achieve the optimum effect for prolong duration of time. All the prepared formulation was subjected to different type of evaluation like, practical yield, particle size, entrapment efficiency, in vitro release study, in-vitro kinetic study and percentage of mucoadhesion. Particle size was determined by image microscope and the average particle size of prepared formulation was found in the range of 90.32±1.8 to 154.55±0.20 µm for all batches .Cumulative percent drug release was found to be maximum for F4 and F9 (90.88±0.59 and92.10±0.414). Formulation F1,F2,F3,F4,F5,F7,F9 show Zero order releases profile and other formulations like, F6 show Hixon, F8 show Higuchi , F 10 show First order kinetic. All the batches showed good in vitro mucoadhesive property. It was also found that the prepared formulations not showing any interaction .The satisfactory result of different evaluatory parameters, reflect that the experimental study will prove to be a effective delivery system.

Keywords :- Mucoadhesion. , Entrapment efficiency, in-vitro kinetic study

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INTRODUCTION

The oral route is considered as the most promising route of drug delivery. It has various advantages such as ease of administration, low cost therapy, versatility and patient compliance. [1-6]The oral drug delivery depends on various factors such as type of delivery system, disease condition, patient condition, duration of the therapy and the physicochemical properties of the drug. Convectional drug delivery system having many disadvantages such as chances of missing frequent administration, a typical peak plasma concentration time profile, difficult to attainment steady state condition, unavoidable fluctuation in the drug concentration etc. which may lead to improper control on diseases condition.[7.8]

During the last two decades the development of mucoadhesive controlled-release dosage forms has gained considerable interest.[9] The idea of using bioadhesive polymers to prolong the contact time in the mucosal route of drug delivery was introduced in early 1980s, and since then it has attracted considerable attention from pharmaceutical scientists. The concept of mucoadhesive drug delivery is based on the bioadhesive property of certain polymers that becomes adhesive on hydration and hence can be used for localizing the drugs to a particular region of gastrointestinal tract and to extend the gastric residence time[10].

Among the several mucoadhesive delivery systems, Microsphere shows its potency as compare to other drug delivery system by virtue of their small size and efficient carrier capacity. Bioadhesive microspheres have major advantages like efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer and specific targeting of drugs to the absorption site.[11-16]

Literature shows that some of the major diseases like cardiac disorder, different life style diseases like high blood pressure, diabetes, obesity, COPD etc are the most common problems of today's societies. For proper management of this type of disease we essentially required such a dosage regimen which may shows appropriate disease control for required duration of time. Diabetes is one of the major causes of death and disability in the world. The latest, who estimate for the number of people with diabetes worldwide, in 2000, is 171 million, which is likely to be at least 366 million by 2030.[17]

Metformin HCL is a biguanide oral antihyperglycemic (antidiabetic) agent. It is used as monotherapy as an adjunct to diet and exercise for the management of type 2 (non-insulin dependent) diabetes mellitus in patients whose hyperglycemia cannot be controlled by diet alone.[18] It is slowly and incompletely absorbed from the gastrointestinal tract, with its absolute

bioavailability reported to be about 50 to 60%.[19, 20] It has a short half life (1.5-4 hrs) and is absorbed from upper intestine within 6 hrs, so repeated administration is required to maintain effective plasma concentration. [21-23]

In consideration of the above fact the present research work has been designed to prepare sustain release mucoadhesive antidiabetic microspheres of metformin HCL by using ethyl cellulose, carbopol 934 in different ratios as polymers. Emulsification/Evaporation method is used for the preparation of microsphere. This formulation serves the problem of convectional formulations and to provide the safety and easy treatment to the patient of diabetes.

MATERIALS AND METHODS

Pure drug Metformin hydrochloride obtain from Abhilasha pharmaceutical as a gift sample, Carbopol 934 and Acetone were purchased from Sd fine –chem limited, Ethyl cellulose, Petroleum Ether and Span 80 were purchase from Samar pharmaceutical industry and Light liquid paraffin from Fizmerk india chemical (India). Other essential machineries, sophisticated instruments, and experimental setup were provided by research center Columbia institute of pharmacy, Raipur.

Method of Formulation

The Metformin HCL mucoadhesive microspheres were prepared by emulsification/evaporation method. Accurately weighed quantity of ethyl cellulose (Table 1) was dissolved in acetone; drug and carbopol 934P powder were added to the ethyl cellulose solution with constant stirring for 24 hours. Than the suspension was slowly dispersed in 40 ml light paraffin containing span 80 at a stirring rate of 80 -100 rpm using mechanical stirrer.[24]

Table 1:-Formulation Table .

S.n	Ratio	Form. No	Drug	Ethyl cellulose	Carbopol 934	Acetone	Light paraffin	Span 80
1	1:1	F1	500 mg	250 mg	250mg	20 ml	40 ml	0.128-0.192 ml
2.	1:1	F2	500 mg	200mg	300mg	20 ml	40 ml	0.128-0.192 ml
3	1:1	F3	500 mg	300mg	200mg	20 ml	40 ml	0.128-0.192 ml
4	1:1	F4	500 mg	166.7mg	333.3mg	20 ml	40 ml	0.128-0.192 ml
5	1:1	F5	500 mg	333.3mg	166.7mg	20 ml	40 ml	0.128-0.192 ml
6	1:2	F6	500 mg	500mg	500mg	20 ml	40 ml	0.128-0.192 ml
7	1:2	F7	500 mg	400mg	600mg	20 ml	40 ml	0.128-0.192 ml
8	1:2	F8	500 mg	600mg	400mg	20 ml	40 ml	0.128-0.192 ml
9	1:2	F9	500 mg	333.33mg	666.6mg	20 ml	40 ml	0.128-0.192 ml
10	1:2	F10	500 mg	666.6mg	333.3mg	20 ml	40 ml	0.128-0.192 ml

EVALUATION OF MUCOADHESIVE MICROSPHERE

Production Yield or Percentage Practicle Yield :

The percentage of production yield was calculated from the weight of dried microspheres (W1) divided by the sum of initial dry weight of starting materials (W2) following formula given below :-[25-,27]

Drug Entrapment Efficiency:

100 mg of microspheres was dissolved in 100 ml of water for 24 hr. Then the solution was sonicated and filtered and the absorbance was measured spectrophotometrically after suitable dilution at 218 nm. The amount of drug entrapped in the microspheres was calculated by the following formula. [28-30.]

$$DRUG\ ENTRAPMENT\ EFFICIENCY = \frac{AMOUNT\ OF\ DRUG\ ACTUALLY\ PRESENT}{THEORETICAL\ DRUG\ LOAD\ EXPECTED} \times 100$$

Particle Size:

Particle size of the micro particles was determined by digital image microscope. Approximately 10 micro particles in each batch were used for the study and the mean particle size and standard deviation was determined.[31,]

In Vitro Dissolution:

The *in-vitro* release study of drug loaded microspheres was carried out at 50 rpm using in USP dissolution apparatus (Type1) under sink conditions. Around 100 mg of microspheres was added to dissolution medium (900 ml of water). At every 1 hr time intervals, 10ml sample was withdrawn and replaced by an equal volume of fresh dissolution medium. The samples were than subjected for suitable dilution and analyzed spectrophotometrically at 218 nm. The concentration of Metformin in test samples was measured and calculated using a regression equation of the calibration curve.[34-,38]

In vitro kinetic study:

Drug transport from pharmaceutical dosage forms involves multiple steps provoked by different physical or chemical phenomenon, making it difficult to get a mathematical model that describing it in the correct way. The release models with major application and best describing drug release phenomena are, in general, the Higuchi model, zero order model, first order model and Korsemeyer-Peppas model. These mathematical models give the drug release pattern from dosage forms. Formulas for mathematical model calculation are given below.[39]

Zero order release kinetics $Q = Q_0 + K_{0t,}$

First order release kinetics $dC / dt = k (C_s - C_t)$

Hixson-Crowell cube root law $Q_{01/3} – Q_{t1/3} = KHC_t$,

Higuchi Model Qt = kH (t) 0.5

Korsmeyer-Peppas Model, Mt/M N = Ktn.

Mucoadhesive Test

The mucoadhesive property of microspheres was evaluated by in vitro wash off test for mucoadhesion . A Piece of goat intestinal mucosa were mounted onto glass slide. After that 100 mg of microspheres were spread onto each wet rinsed tissue specimen and immediately therefore the support was hung onto the arm of USP disintegration apparatus. Now operating the disintegration test machine, the tissue specimen was given a regular up and down movement in 6.8 phosphate buffer at 37 ^{o}C. At the end of 1 hr and at hourly intervals upto 5 hrs, the number of microspheres still adhering onto the tissue was counted.[32,33,40]

$$\% \text{ MUCOADHESION} = \frac{\text{NO. OF PARTICLE REMAINS ON MUCOSA}}{\text{NO OF APPLIED MICROSPHERE}} \times 100$$

RESULT AND DISCUSSION

The experimental part of this research was started with different preformulation studies. First the drug subjected to different standard identification test like FTIR study and the observed peak was found within the range of 736 to 1577 cm^{-1}. Melting point of Metformin HCL was found to be 223 to 225^{o}C . which was within the range as reported as in pharmacopoeia, again it was found that the solubility profile of the gift sample were also match with pharmacopoeial standard.

We prepared calibration curve of metformin HCL in different medium, Maximum R^2 value was found in water ie 0.9969.It is because metformin HCL is freely soluble in water. In the present study, total 10 formulations (F1, F2, F3, F4, F5, F6, F7, F8, F9and F10) of Metformin HCL microspheres of different ratios was prepared. In order to select the best formulation, various parameters like Particle Size, Entrapment efficiency, In-Vitro drug release, In-Vitro Kinetic release, percentage of mucoadhesive were performed. Production yield of the formulation was found in the range of 77.77 % to 94 %.

The entrapment efficiencies of all formulation are showed in Table 2, It was observed that increase in the concentration of the polymer increase the entrapment efficacy. This may be due to increase in the viscosity of the solution, which increases the strength matrix formation. On the basis of entrapment efficiency result, it may conclude that F10 shows comparatively higher entrapment efficiency (Figure 1). Small amount of microspheres of each batch were sighted on the slide and observed under digital image microscope. The average particle size was calculated. The mean size (diameter) range of microspheres was found to be between 90.32±1.8 to

154.55±0.20 µm for all formulations (Table 2). Increase in the particle size was observed with increase in polymer concentration that might be due increased polymeric mass(Figure 2).

Table 2 :Characterization of Metformin Hcl microspheres.

S.no	Formulation code	Entrapment efficiency	Particle size (diameter)	% of Mucoadhesion	Production Yield
1	F1	63.51±5.57	90.32±1.8	63.33±4.71	93.4±0.95
2	F2	63.51±5.57	91.25±1.19	66.66±4.71	89.83±0.28
3	F3	67.93±3.48	97.593±0.12	61.66±3.49	94.93±2.42
4	F4	43.33±7.61	103.07±1.42	69.44±4.90	92.43±1.69
5	F5	70.16±11.59	104.72±0.59	59.33±5.83	93.8±2.52
6	F6	79.04±6.42	106.75±0.23	76.11±4.90	80.44±5.34
7	F7	76.44±6.16	109.10±1.89	82.22±5.44	90.22±3.15
8	F8	82.38±4.17	117.06±0.64	73.88±4.90	77.77±3.79
9	F9	74.07±8.25	137.96±0.16	89.44±4.43	90.0±.002
10	F10	85.78±9.65	154.55±0.20	70.55±4.90	88.4±3.07

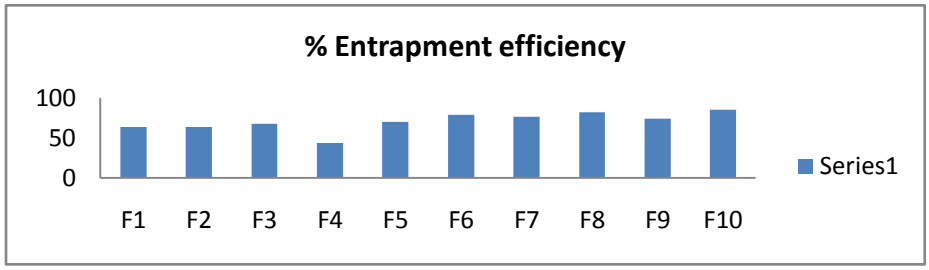

Figure 1:- Entrapment Efficiency

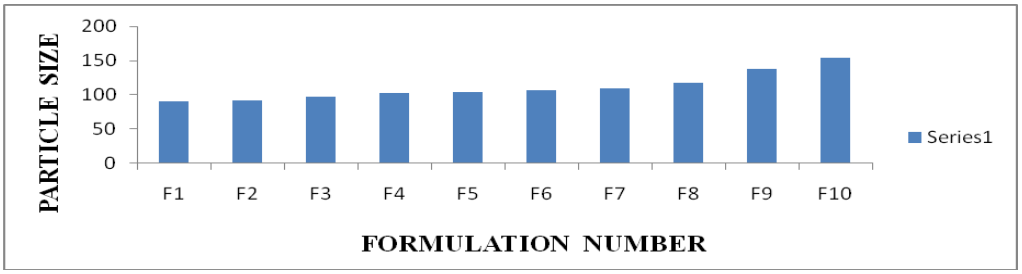

Figure 2:- Particle Size.

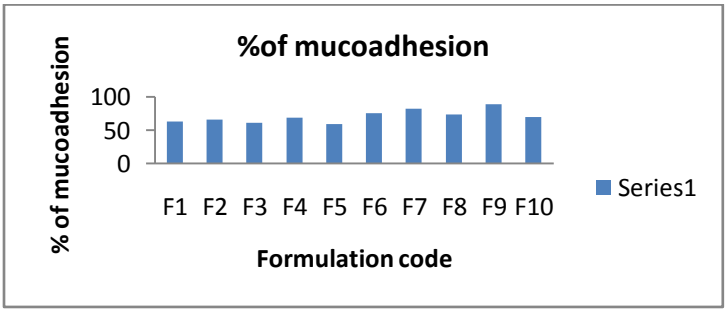

Figure 3:- Percentage of Mucoadhesion

In -Vitro drug release studies (for 12 hrs.) were carried out for all formulations;[F1to F10] were determined and found respectively 86.58±3.33, 83.69±3.17, 63.92±2.56,80.55±2.33, 72.97±1.13,

90.88±0.59 , 69.29±2.75, 83.69±3.17, 72.71±3.73 , ,92.10±0.414 (Figure 4).On the basis of drug release it was found that formulation F6 and F10 were shows comparatively better performance. Drug release Kinetic studies of all formulation were performed on the basis of mathematical modeling and resultant data are graphically represented. It was found that almost all the formulations follow zero order drug release profile but the drug release phenomena of some formulation varies from each other (shown in figure 5,6,7,8)

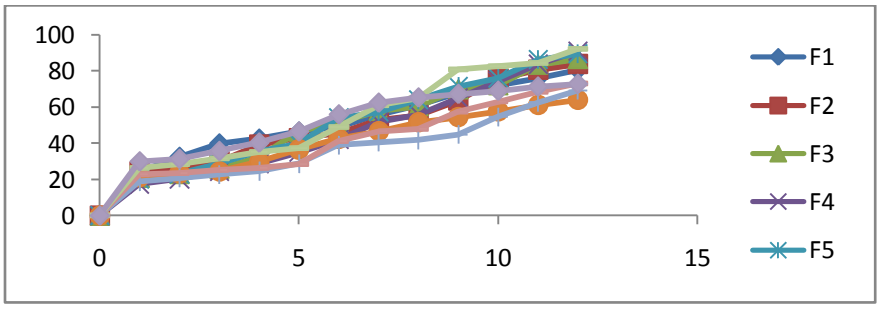

Figure 4:-In Vitro Release Study .

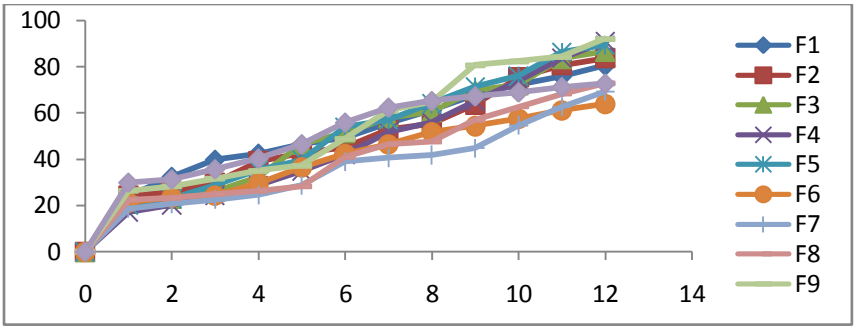

Figure 5 :- zero order kinetics :-

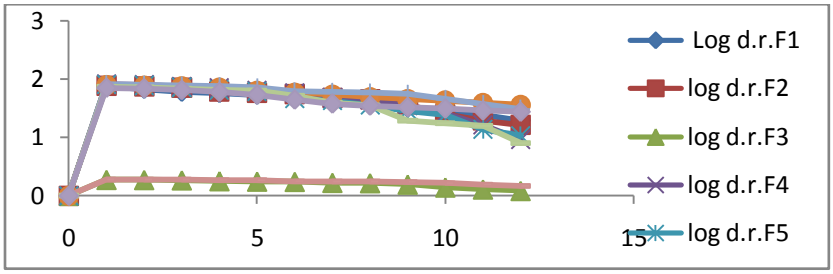

Figure 6 :- First order kinetics :-

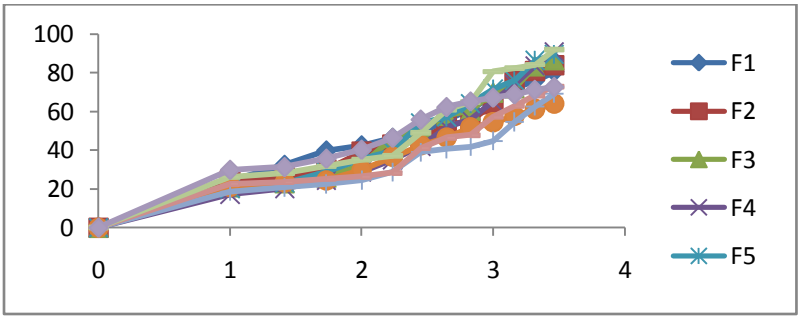

Figure 7 :- Highuchi classical diffusion :-

The drug polymer incompatibility study of the prepared formulations were subjected to FTIR study. It was found that formulation peak was matched with the drug peak, and no changes were observed in the place of peaks, hence it can be conclude that polymers are compatible with the drug. The percentage of mucoadhesion of all formulation was increases with increase in the concentration of Carbopol 934(Figure 3).

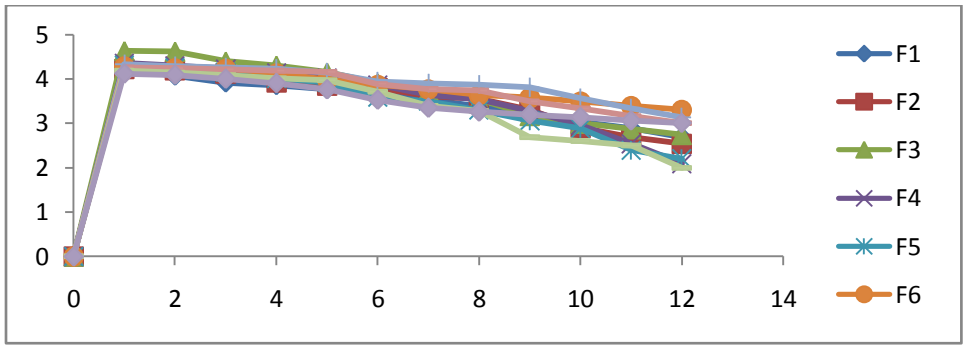

Figure 8:- Hixon crow well cube root method

CONCLUSION

Metformin HCL sustained release mucoadhesive microspheres were successfully prepared by emulsification/evaporation method. The concentration of Carbopol 934 and ethyl cellulose affected the dependent variable such as percentage of mucoadhesion, drug entrapment efficiency etc. As a polymer concentration increase percentage mucoadhesion and drug entrapment efficiency also increases. The mucoadhesive microspheres exhibited good mucoadhesive property and in- vitro release. In context of different parameters it may be concluded that F10 (1:2 ratio) formulation shows comparatively better results. These sustained release mucoadhesive microspheres formulation may fulfill the need of diabetics patients those who regularly consume the drug orally. Further work need to be carried out for find out the reproducibility and establish the experimental data's.

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