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Original Article

ENHANCEMENT OF THERAPEUTIC WINDOW OF METFORMIN HYDROCHLORIDE BY FABRICATION OF MICROSPHERES COMPRISING POLYMERIC INCULCATION WITH SEMI-SYNTHETIC AND SYNTHETIC POLYMERS BY IMPLEMENTATION OF BOX-BEHNKEN DESIGN

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ABSTRACT

Objective: Innovative enhancement of therapeutic window of Metformin hydrochloride (MFH) and bioavailability through mucoadhesive microspheres by polymeric inculcation of hydroxypropyl methylcellulose K4M grade (HPMC K4M), hydroxypropyl methylcellulose K100M grade (HPMC K100M) and Kollidon SR grade (KS).

Methods: Controlled release system was developed by incorporating semi-synthetic and synthetic polymers by modified solvent evaporation technique. Fabrication of mucoadhesive microspheres was designed by the implementation of experimental designs to obtain most optimum concentration of selected factors. The method was optimized by Box Behnken design (BBD) with selected factors as concentrations of semi-synthetic and synthetic polymer with stirring speed influence for the obtained responses that were mean particle size (Y1) entrapment efficiency of drug (Y2) and percent mucoadhesion (Y3). Microspheres were characterized for particle size, entrapment efficiency of drug, ex-vivo mucoadhesion study, *in vitro* study, Fourier transform infrared spectroscopy (FTIR), x-ray diffraction (XRD) detection and H^1 Nuclear magnetic resonance (NMR) quantification for optimized formulation.

Results: Implementation of response surface method software for BBD yielded stable microspheres with mean particle size 274 µm, entrapment efficiency of drug 85.07% and percent mucoadhesion 67.03% for optimized formulation F5.

Conclusion: Bridging of MFH with the highly innovative combination of semi-synthetic and synthetic polymers yielded stable, cost-effective microspheres with improved bioavailability with controlled-release effect as till date no literature is available that provide information with selected polymeric combination and analytical characterization.

Keywords: Box-behnken design, Controlled release system, Kollidon SR, Metformin hydrochloride, Nuclear magnetic resonance

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INTRODUCTION

Selection of drug is the most optimum parameter in designing of a particular dosage form. In our research, we had focused on such a drug that has multivariate effect with minimum side effects. MFH was selected as a model drug in present research work. MFH is the most felicitously picked alternative in treatment of non-insulin dependent diabetes mellitus (NIDDM. It is an orally administered, anti-hyperglycemic biguanide drug [1-4]. MFH has numerous other applications in drug therapy including emendation of menstrual cycles by making them more regular and enhances fertility in women. It is also used in patients with polycystic ovarian syndrome (PCOS) [5, 6]. It has anti-tumor effect on colon, ovaries, pancreas, breast and lungs cancer cells, hence, it has strong anti-proliferative effect [7], possesses anti-oxidant activity, shows high efficacy in diabetic nephropathy [8]. Several research articles revealed that MFH also exhibits good cardiovascular protective effect that was independent of its glucose lowering efficacy [9, 10]. There are some minor side effects including stomach pain, nausea, vomiting, diarrhea, muscle pain with major adverse effect includes ketoacidosis, hence the drug should be prohibited to patients with impaired kidney functioning due to occurrence of lactic acid acidosis, and otherwise it is the first line treatment drug in patients associated with diabetes mellitus either alone or in combination with other glucose-lowering drugs [11]. MHF is a biguanide white to off-white compound having molecular weight 165.63 and molecular formula $C_4H_{11}N_5 \cdot HCl$ (Imido dicarbo nimidic diamide, *N*, *N*-dimethyl-,monohydrochloride; 1,1-Dimethylbiguanide mono hydro chloride) with absolute bioavailability of 50-60% and plasma half-life of 1.5 h to 4.5 h, the therapeutic window of MFH in plasma lies between 01 and 50 µM [12]. On oral administration, there exists an incomplete gastrointestinal absorption of MFH with absolute bioavailability of 40 to 60 % and rapid elimination, hence the administration of a controlled release (CR) formulation of MFH would be beneficial to maintain the optimum therapeutic window of drug and minimize dosing frequency due to short half-life so enhanced patient acceptability will be obtained [13]. In this research we had tried to develop a polymeric inculcation of semi-synthetic and synthetic polymers for CR of MFH by microspheres fabrication. The semi-synthetic polymer selected was HPMC, also known as hypromellose, it is one of the best known semi-synthetic non-ionic cellulosic, biocompatible and viscoelastic polymer with unique property of high water absorption and retention capacity. There were several grades of hypromellose available, the composition differs due the substitution of methyl and hydroxyl propyl group present in the structure [14]. The selected HPMC grades in our research comprised of HPMC K4M and HPMC K100M as synthetic polymers in fabrication of CR formulation of MFH. The combination of both grades had been opted as they yielded high swellability, as soon as they encounters with water or simulated gastric fluid they develop a viscous gel layer and results in CR of drug from HPMC matrices. HPMC K4M has strong mucoadhesive property whereas HPMC K100M has high gastro-retentive nature [15, 16]. The another desirably chosen polymer for our research was KS, it comes under the category of synthetic polymer, the sustaining capacity of drug in matrix formulation makes KS an ideal candidate in fabrication of CR formulations along with improved bioavailability [17, 18]. As our focus in this research was to enhance the therapeutic window of MFH through incorporating the drug with semi-synthetic and synthetic polymeric inculcations of matrix yielding CR of drug, we tried to design mucoadhesive microspheres of MFH to increase the residence time of formulation in the stomach. The narrow therapeutic window and short half-life of MFH make it a suitable candidate to be designed as mucoadhesive microspheres for

enhancement of therapeutic index, improved bioavailability and reduced side effects [19]. The interpenetration of polymer molecules to mucosal membrane was higher with low molecular weight polymers whereas with higher molecular weight entanglement will be obtained, hence a combination of low and high molecular weight polymers were selected to obtain improved effect [20, 21]. So, in our research we had selected different grades of HPMC as opted semi-synthetic polymer to obtain good mucoadhesive, gastro-retentive (GR) and CR effect along with enhanced CR effect of KS as the synthetic polymer for fabrication of MFH loaded mucoadhesive microspheres. Literature revealed numerous research and review articles on MFH, in one study performed by Karna S *et al.*, 2016, they had prepared GR, swellable and floating sustained release tablets. They had fabricated the tablet formulation by incorporating HPMC, xanthan gum, sodium alginate, carbopol and ethyl cellulose. The prepared formulation was also found to be stable for tenure of three months [22]. The study conducted by Quazi M A *et al.*, 2020, revealed formulation of MFH loaded microspheres comprising of natural and synthetic polymer for comparative analysis. The result revealed enhanced flow properties with higher drug entrapment efficiency for microspheres fabricated with synthetic polymer Carbopol as compared with formulation designed with natural polymer sodium alginate [23]. The present research study involved fabrication and characterization of MFH microspheres inculcating semi-synthetic and synthetic polymers by employing response surface methodology and implementing Box-Behnken design (BBD). BBD was selected from the ocean of various available experimental designs and applied to statistically optimize the formulation to improve therapeutic index and bioavailability of drug by enhancement of entrapment efficiency and CR of MFH in this study. The selected variables were HPMC K4M concentration (A), HPMC K100M concentration (B) Kollidon SR concentration (C) and stirring speed (D) along with selected response variables as mean particle size (Y1) percent entrapment efficiency (Y2) and percent mucoadhesion (Y3) of fabricated microspheres with predetermined level values for these variables estimated by trails according to factorial design [24, 25]. The selected method is highly innovative, especially the optimization of formulation parameters by following response surface method as till date there does not exists any literature reporting mucoadhesive microspheres of MFH with combination of HPMC K4M, HPMC K100M and KS fabricated by modified solvent evaporation technique. This makes our research work highly novel and discrete from the available literature with characterization of optimized formulation by latest modern analytical techniques incorporating estimation of particle size, entrapment efficiency of drug, percentage mucoadhesion, *in vitro* drug release profile, drug polymer interaction analysis by FTIR, physical state estimation of drug by XRD detection and NMR based quantification.

MATERIALS AND METHODS

Chemicals and reagents

Metformin hydrochloride was obtained as a gift sample from Aurobindo Pharmaceuticals Ltd, Hyderabad, India, HPMC K4M and HPMC K 100M were received from S D fine chemicals, Mumbai, India, Kollidon SR was purchased from Natco, Hyderabad, India, All other chemicals used were of analytical grade reagent.

Method of fabrication

Fabrication of MFH loaded microspheres comprising of semi-synthetic and synthetic polymers were produced by contemporaneous application of solvent evaporation and diffusion techniques. Initially, as per the data obtained from RSM software by using BBD, the specified parameters were recorded and employed in microspheres formulation for seven batches from F1 to F7 by following ED. Initially, accurately weighed quantities of MFH, HPMC K4M, HPMC K100M, KS and 0.1% polyethylene glycol were mixed in 1:1 mixture of dichloromethane and ethanol at room temperature. Then the above mentioned slurry was slowly introduced to 80 ml of 0.46% (W/V) polyvinyl alcohol (emulsifier). The system was stirred for three hours by using Remi Lab Magnetic stirrer with speed meter to remove the volatile solvent ethanol at room temperature to produce spherical microspheres. The microspheres were collected by vacuum filtration and washed repeatedly with water. Finally, the prepared microspheres were dried at ambient temperature (25 °C) for 24 h and dried in vacuum chamber at 25 °C for 2 h to remove any residual solvent. All the process variables like concentration of HPMC K4M, concentration of HPMC K100M, concentration of KS and stirring speed were studied during optimization of microspheres and the most optimum concentration with maximum stabilized formulation was recorded as seen in table 2.

Experimental design (ED)

The present research of formulating and characterizing CR microspheres of MFH was mainly focused to improve the therapeutic index of drug by improving bioavailability and residence time of drug within body, as it is drug candidate that comes under the category of comprising low therapeutic window. Design and fabrication was statistically optimized by BBD for various formulation parameters like, maximum drug entrapment efficiency of microspheres and mean particle size. This research was executed by optimization of MFH microspheres through response surface methodology by applying BBD and using Design Expert 12.0.7.0 software (STATEASE Inc., USA), with quadratic design model that yielded 27 experimental runs for present data [26, 27].

Characterization of MFH loaded mucoadhesive microspheres through semi-synthetic and synthetic polymers

Particle size estimation

MFH loaded microspheres were accurately determined by optical microscopic method using calibrated stage micrometer.

Entrapment efficiency of drug

The quantity of pure MFH loaded in fabricated microspheres was investigated by taking 100 mg of prepared formulation in 50 ml of phosphate buffer (pH= 7.4) in volumetric flask then kept on sonicator at 125 W (Imeco sonofier, Imco ultrasonics, India) for two hours to mix uniformly, finally the volume was made up to 100 ml by adding buffer, then again this flask was kept on sonicator for one hour and kept as it is overnight for extraction of drug from microspheres. Then the solution was passed through 0.45 µm membrane filter to collect the filtrate. The respective dilutions were made from this stock solution and absorbance was measured at 233 nm employing UV-visible spectrophotometer (UV-2450 Shimadzu, Japan) against blank. The method was repeated three times.

Ex-vivo mucoadhesive study

The mucoadhesive property of fabricated MFH loaded microspheres were evaluated by taking freshly excised piece of goat stomach mucosa and then they were mounted on glass slides with the help of cyanoacrylate glue and 50 prepared microspheres were spread on the wet rinsed tissue specimen with 4 drops of 0.01N HCl and immediately the slides were hung to the arm of USP tablet disintegration test apparatus with the help of suitable support. Then the disintegration test machine was operated and the attached mucosal specimen was given regular up and down movement in the fluid comprising 800 ml 0.01N HCl (pH = 2.0) at 37±0.5 °C in one liter vessel capacity for various time interval up to 7 h. Then the apparatus was stopped and the number of adhered microspheres to the mucosal tissue were counted [28, 29].

In vitro drug release analysis

The release of MFH drug from the prepared microspheres was studied in 0.1N HCl at pH 1.2 and in phosphate buffer pH 7.4 (900 ml) respectively using a USP six station dissolution (LAB DISSO 2000) rate testing apparatus with a rotating paddle at 50 rpm and 25 cm depth 20 by maintaining temperature of 37±0.5 °C. Sample of 5 ml was withdrawn at various time intervals and subsequently diluted using pH 7.4 phosphate buffer. After suitable dilutions the absorbance was measured at 206 nm for 0.1N HCl and 233 nm for phosphate buffer, using UV-visible spectrophotometer (2450 Shimadzu, Japan) against a blank. The withdrawn sample was filtered through Whatman grade 1 filter paper and diluted to estimate MFH at 233 nm through spectroscopy against blank solution. The quantity of drug was estimated through calibration

curve and release studies were performed in triplicate and the observed data represented in table 6.

FTIR analysis

The detection of any possible interaction between pure drug and optimized formulation of MFH loaded microspheres were scanned through FTIR spectra by using Perkin-Elmer FTIR (spectrum RX).

XRD study

XRD analysis was performed to determine the crystalline characteristic of drug and optimized fabricated microspheres by using X-ray diffractometer (Brucker Axs, 08 Advance) [30].

NMR analysis

The compatibility analysis of fabricated MFH microspheres with incorporated polymers was performed by using proton (H^{1})Nuclear magnetic resonance spectroscope (ECX 400 JOEL, Japan) working at 500 MHz and 300 K with dimethy sulphoxide (DMSO-d6) as solvent for estimation of chemical shift in this experiment.

RESULTS AND DISCUSSION

The present statistically optimized and BBD assisted MFH loaded microspheres were fabricated by employing optimized parameters as represented in table 1 and table 2. The fabrication method was experimentally designed and the data obtained from design for factors A, B and C with their corresponding responses Y1, Y2 and Y3 were explained through fig. 1 and fig. 2 with the corresponding values represented in table 1 and table 2. Finally, analysis of variance (ANOVA) was applied to obtain significant difference from design matrix and the data obtained after implementation of ANOVA was represented in table 3, table 4 and table 5 and were found to be significant. The data obtained from experimental design for factors A, B and C with their corresponding responses Y1, Y2 and Y3 were explained through fig. 1 and 2.

Particle size analysis

It was observed from the obtained data that mean particle size of MFH loaded microspheres ranged between 246.01±0.49 µm to 289.13±0.07 µm for all fabricated formulations, whereas in one study executed by Kesharwani S *et al.*, 2020 [31] they had fabricated MFH microspheres incorporating eudragit and HPMC with particle size range 397±23.22 µm to 595±15.82 µm and entrapment efficiency ranged from (83.49±1.33) % to (60.02±1.65) %. On implementation of BBD to the parameter mean particle size yielded superior microspheres with spherical surface, smaller particle size and microsphere size increased on increasing polymer concentration for all the seven formulations. The mean particle size of 274 µm for F5 formulation was obtained with maximum optimization.

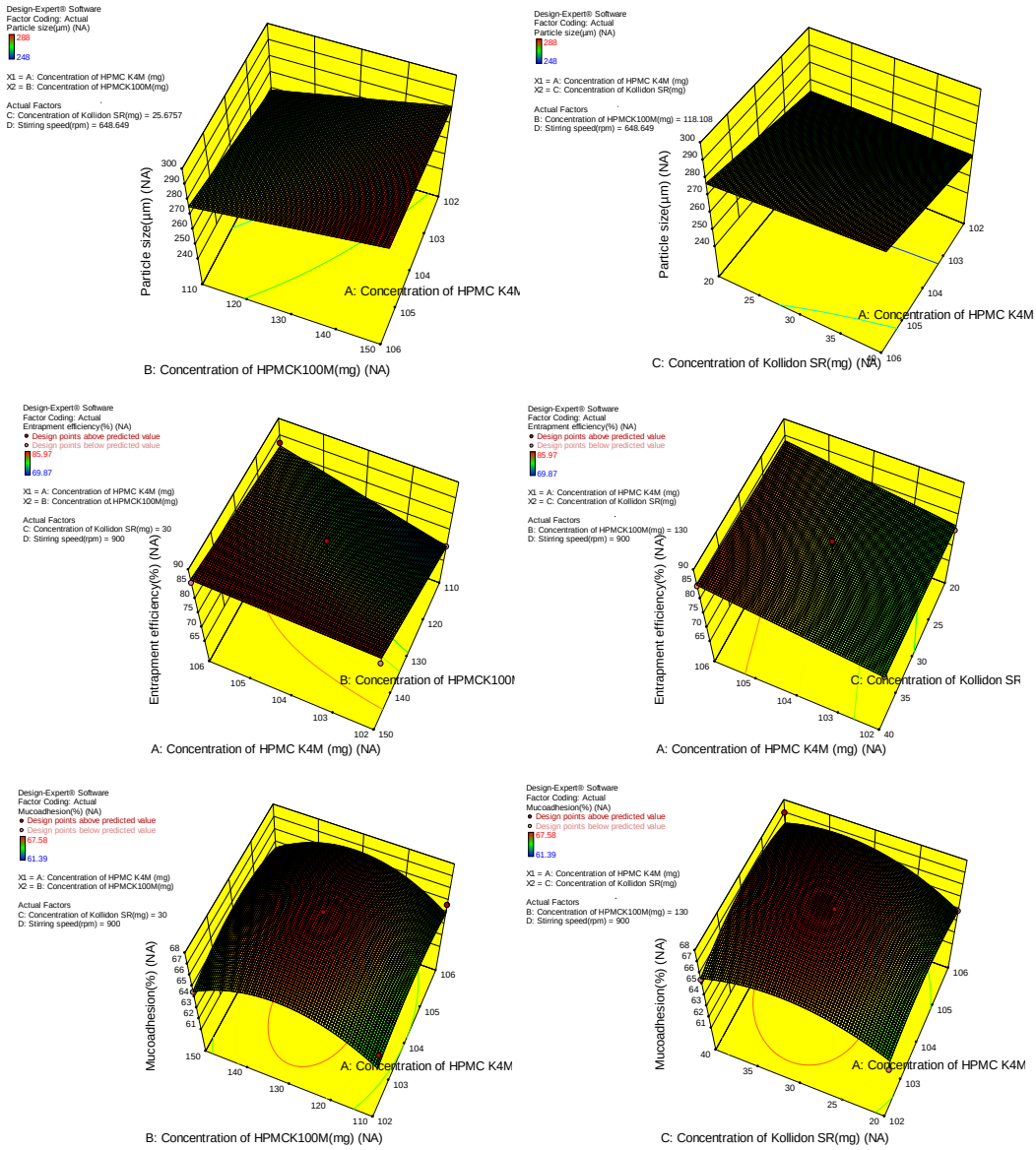

Fig. 1: Three dimensional response surface effects from factors A, B and C with their corresponding responses Y1, Y2 and Y3

Table 1: Data representing optimized fabrication parameters and investigated range during microspheres formulation

Factor	Name	Units	Minimum	Maximum	Low level	High level	Mean	Standard deviation
A	Concentration of HPMC K4M	mg	102.00	106.00	-1 ↔ 102.00	+1 ↔ 106.00	104.00	01.35
B	Concentration of HPMC K100M	mg	110.00	150.00	-1 ↔ 110.00	+1 ↔ 150.00	130.00	13.58
C	Concentration of KS	mg	020.00	40.00	-1 ↔ 20.00	+1 ↔ 40.00	030.00	06.79
D	Stirring speed	rpm	600.00	1200.00	-1 ↔ 600.00	+1 ↔ 1200.00	900.00	203.81

*mean±SD (Standard deviation), n=3

Table 2: Data representing Box-Behnken experimental design layout with selected factors and obtained responses

Std	Run	Factor 1	Factor 2	Factor 3	Factor 4	Response Y1	Response Y2	Response Y3
4	1	106	150	30	900	279	85.73	64.08
10	2	106	130	30	600	283	83.65	64.31
25	3	104	130	30	900	272	84.97	67.58
23	4	104	110	30	1200	248	73.94	61.39
9	5	102	130	30	600	267	78.04	65.27
16	6	104	150	40	900	288	85.03	63.06
14	7	104	150	20	900	281	84.93	64.71
27	8	104	130	30	900	272	84.97	67.58
1	9	102	110	30	900	259	69.87	65.28
15	10	104	110	40	900	266	72.07	64.15
17	11	102	130	20	900	263	75.38	63.74
24	12	104	150	30	1200	264	85.97	64.03
3	13	102	150	30	900	271	84.08	64.61
12	14	106	130	30	1200	279	83.85	65.04
11	15	102	130	30	1200	258	77.43	64.91
19	16	102	130	40	900	263	79.08	65.52
13	17	104	110	20	900	257	72.94	62.47
26	18	104	130	30	900	272	84.97	67.58
2	19	106	110	30	900	274	83.06	64.72
22	20	104	150	30	600	284	85.02	65.53
8	21	104	130	40	1200	279	85.07	66.17
5	22	104	130	20	600	283	83.09	64.72
18	23	106	130	20	900	280	81.85	63.94
21	24	104	110	30	600	265	77.03	64.21
6	25	104	130	40	600	287	85.04	66.32
7	26	104	130	20	1200	261	82.41	62.83
20	27	106	130	40	900	287	84.67	67.03

*mean±SD (Standard deviation), n=3

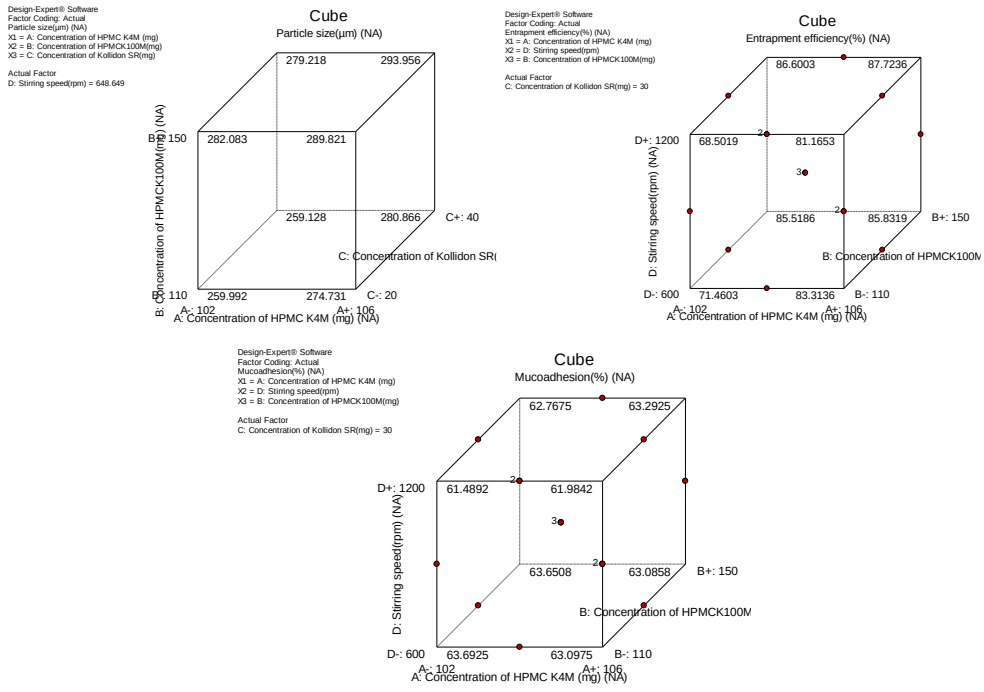

Fig. 2: Representation of cubical design spaces of factors A, B and C on corresponding responses Y1, Y2 and Y3

Table 3: ANOVA data for quadratic model representing response Y1 (mean particle size)

Source	Sum of squares	Df	Mean square	F value	p value	Prob>F
Model	2435.50	10	243.55	6.75	0.0004	
A-Concentration of HPMC K4M (mg)	850.08	1	850.08	23.57	0.0002	Significant
B-Concentration of HPMCK100M(mg)	800.33	1	800.33	22.19	0.0002	
C-Concentration of Kollidon SR(mg)	168.75	1	168.75	4.68	0.0460	
D-Stirring speed(rpm)	533.33	1	533.33	14.78	0.0014	
AB	12.25	1	12.25	0.34	0.5682	
AC	12.25	1	12.25	0.34	0.5682	
AD	6.25	1	6.25	0.17	0.6828	
BC	1.00	1	1.00	0.028	0.8699	
BD	2.25	1	2.25	0.062	0.8060	
CD	49.00	1	49.00	1.36	0.2609	

Entrapment efficiency of drug

The RSM assisted and ED implemented yielded high entrapment of drug in fabricated microspheres corresponding to the following data ranging from (68.04±0.07) % to (85.98±0.01) % for all the formulation from F1 to F7. It was observed that on increase in polymer concentration, the entrapment efficiency of formulation also increased due to higher inculcations with increased polymer concentration and enhanced stirring speed. In present experimentally designed method by BBD, the two selected response were mean particle size and drug entrapment efficiency, so on implementation of selected model for both responses yielded maximum optimized drug entrapment efficiency as 85.07% for F5 formulation with maximum optimization.

Table 4: ANOVA data for quadratic model representing response Y2 (entrapment efficiency)

Source	Sum of squares	Df	Mean square	F value	p value	Prob>F
Model	492.97	10	49.30	6.54	0.0005	Significant
A-Concentration of HPMC K4M (mg)	126.30	1	126.30	16.75	0.0008	
B-Concentration of HPMCK100M(mg)	318.79	1	318.79	42.29	<0.0001	
C-Concentration of Kollidon SR(mg)	8.94	1	8.94	1.19	0.2922	
D-Stirring speed(rpm)	0.85	1	0.85	0.11	0.7409	
AB	33.29	1	33.29	4.42	0.0518	
AC	0.19	1	0.19	0.026	0.8747	
AD	0.16	1	0.16	0.022	0.8846	
BC	0.24	1	0.24	0.031	0.8620	
BD	4.08	1	4.08	0.54	0.4726	
CD	0.13	1	0.13	0.017	0.8987	

Ex-vivo mucoadhesive study

It was observed that as the concentration of mucoadhesive polymers was increased, there was gradual increase in degree of mucoadhesion to the mucosal sample tissue, but with increase in stirring speed the mucoadhesive tendency was reduced. Hence less stirring speed with higher concentration of semi-synthetic polymers yielded enhanced mucoadhesion. The values obtained ranged from (60.09±0.03) % to (68.07±0.05) % for all the formulation from F1 to F7 with 67.03% for most optimized formulation F5.

Table 5: ANOVA data for quadratic model representing response Y3 (percent mucoadhesion)

Source	Sum of squares	Df	Mean square	F value	p value	Prob>F
Model	48.97	14	3.50	3.25	0.0237	Significant
A-Concentration of HPMC K4M (mg)	3.675E-003	1	3.675E-003	3.418E-003	0.9543	
B-Concentration of HPMCK100M(mg)	1.20	1	1.20	1.12	0.3110	
C-Concentration of Kollidon SR(mg)	8.07	1	8.07	7.50	0.0180	
D-Stirring speed(rpm)	2.99	1	2.99	2.78	0.1213	
AB	2.250E-004	1	2.250E-004	2.092E-004	0.9887	
AC	0.43	1	0.43	0.40	0.5395	
AD	0.30	1	0.30	0.28	0.6088	
BC	2.77	1	2.77	2.58	0.1343	
BD	0.44	1	0.44	0.41	0.5364	
CD	0.76	1	0.76	0.70	0.4179	
A^2	5.18	1	5.18	4.82	0.0486	
B^2	27.28	1	27.28	25.37	0.0003	
C^2	11.36	1	11.36	10.56	0.0070	
D^2	11.22	1	11.22	10.43	0.0072	

***In vitro* drug release analysis**

The experimentally designed and optimized MFH microspheres were prepared by modified solvent-evaporation technique by incorporating semi-synthetic and synthetic polymers. The representation of drug release behavior of MFH fabricated microspheres revealed that all preparations from F1 to F7 were able to control the drug release from 04 to 10 h with percent drug release ranging from 96.08% to 91.76% respectively. F5 preparation exhibited 92.81% release profile after duration of 10 h, hence it was selected as optimized formulation. In one study conducted by It was observed that on increasing the concentration of HPMC K100M and synthetic polymer KS, release was decreased. From among all seven

preparations, F5 was selected as most optimized preparation representing better drug release with enhanced bioavailability. Identification of best fitting models was performed by using coefficient of determination (R^2) by placing the data of drug release kinetics. It was observed that for the formulation from F1 to F7 reached greater values for coefficient of determination (R^2) ranging from 0.928 to 0.983 for zero order and release exponent value (n) varied from 1.502 to 2.052. The observed data of Korsmeyer-Peppas model recommended non-Fickian diffusion mechanism for fabricated MFH microspheres can be seen from table 6.

Table 6: Drug release profile for MFH loaded microspheres by incorporating semi-synthetic and synthetic polymers

Formulation code	Correlation coefficient (R^2)				Release exponent (n)
	Zero order	First order	Higuchi model	Korsmeyer model	
F1	0.928	0.736	0.718	0.817	1.502
F2	0.940	0.769	0.825	0.952	1.564
F3	0.931	0.878	0.839	0.840	1.731
F4	0.955	0.926	0.856	0.863	1.908
F5	0.979	0.952	0.898	0.942	2.052
F6	0.973	0.959	0.921	0.949	2.019
F7	0.983	0.968	0.941	0.957	1.977

FTIR study

The FTIR analysis was performed by taking samples of pure drug and optimized formulation comprising of semi-synthetic and synthetic polymers inculcation. It was observed from the obtained spectra that no interaction was present between drug and polymers as no additional peaks were observed, representing stable nature of MFH in formulation, as seen in fig. 3.

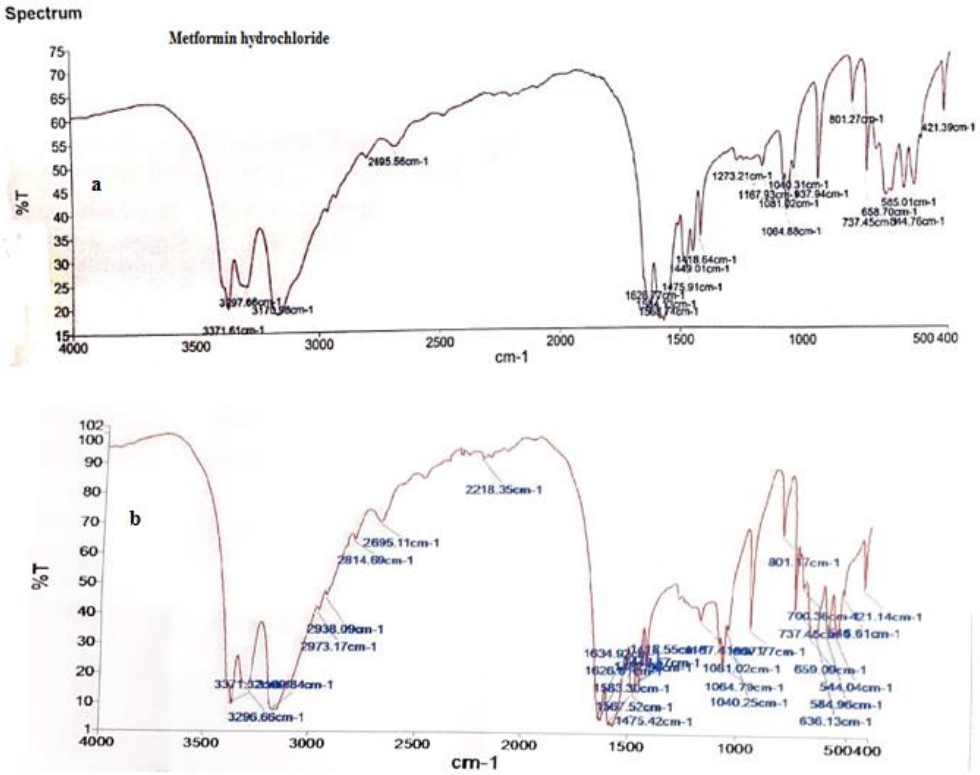

Fig. 3: IR spectra of metformin hydrochloride API (a) Metformin hydrochloride formulations (b)

XRD study

The XRD data reveals the physical state of pure MFH by showing sharp peak, representing its crystalline nature, whereas broad peaks were obtained for polymers representing their amorphous form. The results of diffractogram showed no variation in representative peak intensity height between pure MFH and the optimized formulation F5, exhibiting its crystalline nature. The observed data can be correlated with fig. 4.

NMR analysis

The H^1NMR spectra obtained for optimized MFH fabricated microspheres yielded sharp singlet at 2.92 ppm corresponding to two equivalent methyl groups, this sharp, isolated singlet was chosen as an essential criterion for quantitative determination of MFH. At 6.71 ppm one more singlet was observed due to remaining four protons (2 H from–NH and 2H from–NH_2), another prominent signal at 7.20 ppm was due to the concurrent effect of two protons, one from–NH group and anther from HCl, respectively. The signals obtained at 2.49 ppm and 3.32 ppm were due to presence of residual solvent and water of solvent from DMSO-d6, respectively. The detailed NMR spectrum of fabricated formulation can be correlated to fig. 5 and it represented that all essential chemical shifts of MFH were retained in the formulation, hence exhibiting no interaction between pure drug MFH and the selected semi-synthetic and synthetic polymers.

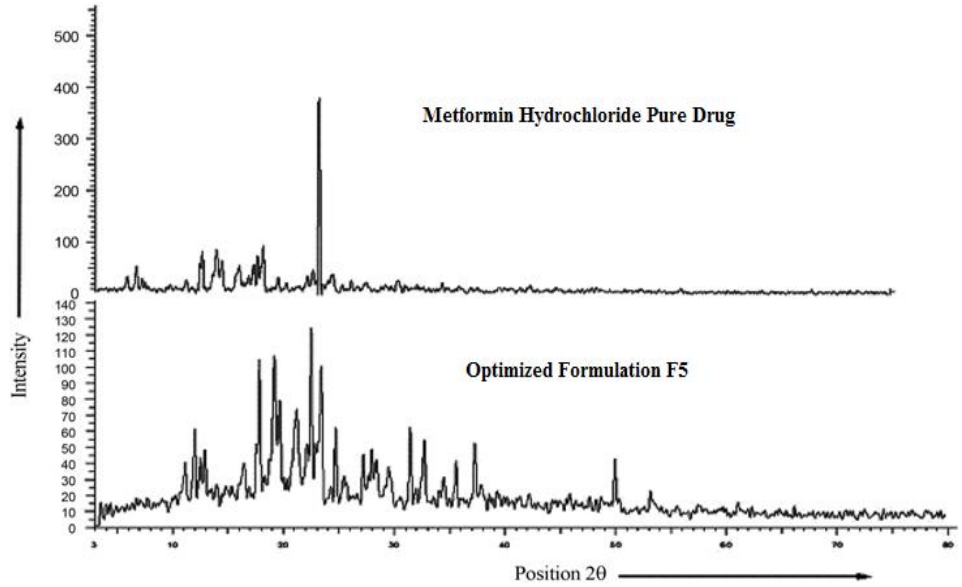

Fig. 4: XRD pattern of pure metformin hydrochloride and optimized formulation F5

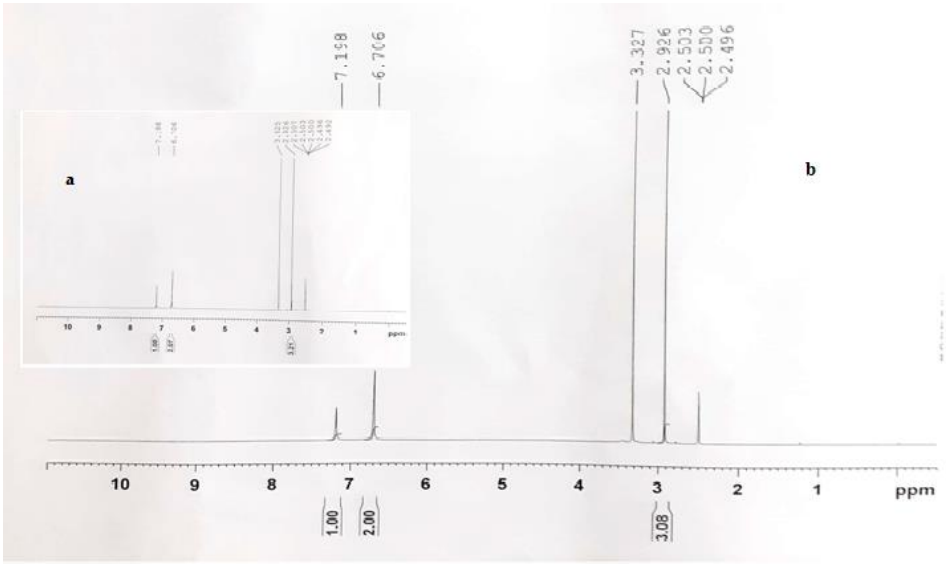

Fig. 5: NMR spectra of metformin hydrochloride API (a) Metformin hydrochloride formulations (b)

CONCLUSION

The BBD assisted optimized MFH loaded microspheres were found to have CR behavior with enhanced flow properties and improved bioavailability as compared with pure drug along with spherical microspheres fabrication with good drug entrapment efficiency and higher mucoadhesive tendency. The modified solvent evaporation technique being uncomplicated, yielded microspheres with improvement in the therapeutic window of drug with stable fabricated microspheres as observed from FTIR and H^1 NMR analysis.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

All the authors declare that there is no conflict of interest by all of us.

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