International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 16, Issue 5, 2024

Original Article

DESIGNING, DEVELOPMENT AND EVALUATION OF GASTRORETENTIVE FLOATING HBS SYSTEM OF METFORMIN: *IN VITRO IN VIVO* STUDIES

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Received: 01 Jun 2024, Revised and Accepted: 17 Jul 2024

ABSTRACT

Objective: The main objective of this study is to formulate, characterized and evaluate the Medium Molecular Mass Chitosan (MMMCH) – Xanthan Gum (XG) based polymeric carrier mediate of non-effervescent floating hydrodynamically Balanced System (HBS) capsule of metformin for developed stomach specific sustain drug delivery over a prolong periods of time.

Methods: Different capsules of metformin were formulated by physical blending of metformin with polymeric mixture to encapsulate in 000 a single unit hard gelatine capsule, than evaluate the different parameters like micromeritics properties, weight uniformity, drug content uniformity, *in vitro* drug release with their kinetics model, DSC and FTIR study, *in vitro in vivo* floating characteristic.

Results: After evaluating the characteristic properties, it was clearly indicated that excellent value ranges, coefficient of weight variation in between 1.39-2.06%, content uniformity of drug in between 98.23-100.05%, *in vitro* drug release in between 60–80 % after 12h that can follow Korsmeyer-Peppas model to release the drug no-fiction diffusion method. FTIR and DSC study exhibit no much more incompatibility between drug and polymer and formation of electrolyte complex help to sustaining release over a prolong periods of time. *In vitro* and *in vivo* floatation study, it was clearly indicated that all formulation (especially MC4) floated in gastric content more than 12h without any floating lag time and excellent *in vivo* buoyancy by the help of x ray images of animal model by replacing the drug with barium sulphate.

Conclusion: So this type of formulation showing great gastroretentive floating drug delivery system in future with another drugs for a prolong periods of time.

Keywords: Gastroretentive, Chitosan, Floating, HBS, FTIR

DOI: https://dx.doi.org/10.22159/ijap.2024v16i5.51674 Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Oral drug delivery system is the most esoteric and preferable way for delivery of drugs till now because of their several advantages like easily administration of drug, patient acceptance and economical [1, 2]. So oral control drug delivery system have great importance for their better gastroretention and effective, sustainable release that can improved the duration of release the drugs as well as raised the bioavailability by reducing wastage and fluctuation of drug [3]. Among the different oral control release drug delivery system, stomach-specific or gastroretentive drug delivery system one of the most important discover and follow in many more years ago but developed in past few decade, including floating drug delivery system [4-6], high-density drug delivery system [7], mucoadhesive/bioadhesive drug delivery system [8, 9], super porous hydrogel drug delivery system [10, 11], magnetic drug delivery system [12], swellable drug delivery system [13], raft forming drug delivery system [14], expendable and unfoldable drug delivery system [15, 16]. These gastroretentive designing dosage forms retain on the gastric region (Upper part of intestine/stomach) for prolong periods of time and release the drug slowly for long time at a constant rate [17]. Floating drug system containing non-emervescent hydrodynamically balance system (HBS) capsules play significant role in recent day of all drugs specially those are absorbed in stomach or small intestine. HBS capsule of drug and hydrophilic polymer form hydrogel and retain float for long lime in our gastric content of stomach [18, 19]. The current work are designing to formulate and evaluate a gastroretentive non effervescent HBS floating capsule of metformin with Medium Molecular Mass Chitosan (MMMCH) and Xanthan Gum (XG) for stomach-specific sustain drug delivery.

Metformin are the drug that are used to treat type–II diabetics mellitus having low bioavailability and moderate biological half-life that will reported previously [16, 20] and also reported many work by taking metformin with HPMC, PEO, CHITOSAN and any other polymer in this field recently [16, 20-23] but here we have to design metformin with medium molecular mass chitosan and Xanthan gum, MMMCH is a commonly used polysaccharides preferred in sustain drug delivery another XG is a natural biopolymer and both are biocompatible and biodegradable to form hydrocolloid gelling floating system that help to float in specific region of stomach for prolong periods of time and sustainly deliver the drug [24-28]. It also previously reported that chitosan-carboxymethyl tamarind gum in situ polyelectrolyte complex based floating capsule of ofloxacin: *in vitro-in vivo* studies [29, 30] but here we have to designing electrolyte complex by taking cationic MMMCH and anionic natural polymer XG that is totally new. So in this investigation we have to design and developed non-effervescent HBS capsule of metformin with MMMCH and XG to evaluate the many more characterization like content uniformity of drug, drug release (*in vitro*), flotation (*in vitro*) in the gastric fluid, *in vivo* gastro retention through X-ray radio image by rabbits and also checkout the drug polymer compatibility by using FTIR and DSC for sustain release of metformin for prolong periods of time.

MATERIALS AND METHODS

Materials

All of the materials and chemical used in this research work were collected from several sources and having good analytical grade. Drug Metformin obtain from Ajanta Pharmaceutical Private Limited. Xanthan Gum and Medium Molecular Mass Chitosan obtain from Sigma Aldrich. Lactose, talc, magnesium stearate and barium sulphate obtain from Loba Chemical Private Limited. 000 size empty hard gelatine capsules obtain from B. S. Trader Private Limited and any other materials purchased commercially from market.

Preparation of metformin floating HBS capsule

Generally, metformin HBS floating capsules was prepared by simple mixing (Blending) of metformin with polymers like XG and MMMC with their appropriate quantities, then mix other excipients like lactose as a diluents, talc as a glidant and magnesium stearate as a

lubricant with this drug-polymer mixture for some time. Finally the mixture of metformin, MMMCH, XG, lactose, talc and magnesium stearate carefully filled by 000 size hard geelatin capsule with special precaution for maintaining the drug content and weight uniformity. The quantity of different metformin HBS capsule is given in the following table 1.

Table 1: Formula of different metformin (HBS) capsules

Ingredients	Formulation code				
	MC1	MC2	MC3	MC4	MC5
Metformin	500	500	500	500	500
MMMCH	25	50	75	100	125
XG	125	100	75	50	25
Lactose	85	85	85	85	85
Talc	5	5	5	5	5
Magnesium stearate	10	10	10	10	10

Hydrodynamically Balanced System (HBS)

Determination of micromeritic properties

It is important to determine the micromeritics properties of the powders samples like drug, polymers, excipients and their mixture for characterized their flow ability that could help to develop the all HBS capsules of metformin. There are several parameters for checking the micromeritic properties as below [6].

Bulk density (BD)

For determination of bulk density, first we can take the required quantity of powder sample from each formulation and weight for determination of mass, then transfer it to a 100 ml of measuring cylinder for determination of initial volume of the powders in cm^3. Then bulk density will be calculated by given formula.

$$BD = \frac{\text{weight of the powder}}{\text{volume of powder before tapping}}$$

Tapped density (TD)

Similarly for determination of tapped density we can take the required quantity of powders from each formulation and weight for determination of mass then transfer it to a 100 ml of measuring cylinder and attached to tapping instruments for determination of tapped volume of the powders in cm^3. Then tapped density will be calculated by given formula.

$$TD = \frac{\text{weight of thepowder}}{\text{volume of the powder after tapping}}$$

Compressibility index (CI)

Carr's index is used to check the compressibility of the powder sample. It is calculated by using the value BD and TP in the given formula.

$$CI = \frac{(TD - BD)}{TD} \times 100$$

Hausner's ratio (HR)

Hausner's ratio is used to check the flow ability of powder sample, similarly using value of BD and TD by using the following formula.

$$HR = \frac{TD}{BD}$$

Angle of repose (AOR)

It is the most important method for checking the flow properties of powder sample. Angle of repose may be defined as maximum angle produced between the pile surface of the powder and horizontal surface of the tile by conducting this process first quantity sample of powder are taken and it will be introduced in a funnel that will be set with the help of stand above the 5 cm of tile surface then a heap angle of powder sample over the tile surface will be produced. Now the AOR was calculated by given formula.

$$\text{Tan } \theta = \frac{h}{r}$$

$$\text{or } \theta = \text{Tan} - 1\frac{h}{r}$$

(Here θ = angle of repose, h = pile height, r = tile surface radius)

Determination of weight uniformity

For estimation of weight uniformity of prepared capsule by taking capsule of 20 numbers in each formulation and weight suitably by using analytical electrical balance that should help to determining the average or mean weight of the capsule. Then calculate the weight variation or % coefficient variation by using this formula [23].

$$\%\text{ coefficient variation} = \frac{\text{standardeiation}}{\text{mean or average weight}} \times 100$$

Evaluate content uniformity of drug

For evaluating drug content of metformin HBS capsule by emptying 10 capsules in each formulation and separately introduced in a beaker containing simulated gastric fluid having pH 1.2; then this beaker containing sample will stirred with the help of magnetic stirrer by maintaining temperature 37±0.5 °C at a speed of 500 rpm for 1 h. Then this sample was filtered by using filter paper (I grade Whatmann^R) after that drug content was analyzed by using a spectrophotometer (Double beam UV-VIS spectrophotometer) at a wavelength of 234 nm against a blank sample.

Determination of *in vitro* release data of drug

In vitro drug release data of metformin HBS capsule in 0.1 N HCL (ph-1.2) was determined by using a dissolution instrument (USP type II) with maintaining speed 50 rpm at 37±0.5° temperatures. At first one capsule of metformin was transferred to the 900 ml 0.1 N HCL (ph-1.2) containing basket rotational dissolution instrument then at the intermediate time interval 5 ml of sample withdraw from the dissolution medium and same quantity of fresh 0.1 N HCL (ph-1.2) was added for maintaining sink condition. Now this withdraw sample from the dissolution medium was diluted and filtered by using Whatmann^R filter paper and estimate the amount of metformin release using a spectrophotometer (Double beam UV-VIS spectrophotometer) at a wavelength of 234 nm against a blank sample [19].

Determine kinetics data of *in vitro* drug release

For determination of *in vitro* release kinetics mechamism of HBS capsule of metformine, the *in vitro* release data of metformin capsules were fitted to mathematically curve fitted kinetics models like zero order, first order, higuchi korsmeyer peppes and Hickson-crowell model [6]. We observed the n value that will express the release mechanism of drug. If the n value is less than or equal to 0.5 then this is called ficken diffusion-controlled release mechanism, if the value ranges between 0.5 to 1 then this is called a non-ficken release mechanism and if the value greater than or equal to 1 than it refer to case-II transport or release [19, 23].

Determine FTIR characterization

The different sample like drug (metformin), polymer (xanthan gum, medium molecular mass chitosan), and drug-polymer mixture (MC4) were tested by using of potassium bromide pellets (IR-grade) in a Fourier transform infrared spectroscopy instrument (Alpha II compact FTIR Spectroscope, Germany). The potassium bromide pellets holding samples were introduced in sample holder, separately. The spectroscopy scanning was determined within range of 4000-500 cm^{-1}.

Determine DSC characterization

The different sample like drug (metformin), polymer (xanthan gum, medium molecular mass chitosan), and drug-polymer mixture (MC4) was tested for Differential Scanning Calorimetry instrument (DCS-3, Mettler Toledo, Switzerland) by placing the sample in an AI pan with heating at 50 °C/min with indium in the reference pan by producing the nitrogenise atmosphere up to ranges of 400 °C.

Determination of *in vitro* floatation

For determination of *in vitro* floating ability of metformin HBS capsule, immersed the best formulation (MC4) in 500 ml of 0.1 N HCL (pH 1.2) in a galas beaker at maintaining 37±0.5 °C temperatures for required time. Then, visually notice the capsule was float/buoyancy on simulated gastric fluid (pH1.2) in particular duration of time and noted the time periods for express about the floating periods of this capsule [23].

Determination of *in vivo* buoyancy through x-ray radio photography

For *in vivo* gastroretention studies conducted by using New Zealand white rabbit through x ray radio photography of this capsule [29, 30]. This experiment was carried out (X-radio imaging) according to Institutional Animal Ethics Committee (Registration no-PCP/IAEC/2023/JAN/20) by the scrutiny of Committee for the purpose of control and supervision of experiment on animal (Registration no-1698/Re/S/13/CPCSEA). For this experiment, we use 2.75±0.25 Kg weight male rabbits (from animal house of Patel College of Pharmacy) the rabbit was taken in suitable room by supplying food and water to adopt this environment. Then this rabbit holds overnight (encaged) without food before the experiments. Then conduct the experiment from early morning 6 pm to evening 6pm for completion and minimize the suffering of animal only by supplying sufficient water. Here the formulation MC4 will replace drug to $BaSo_4$ and introduced in rabbit mouth with the help of tube flushing water carefully. Then x ray photography of gastric region in rabbit was capture at 3, 6 and 12 h time intervals [16, 29, 30].

Determination of statistical analysis

Obtaining all data should be analyzed in Microsoft Excel and the determination of curve fitting release kinetics; we used Kinet Ds software for *in vitro* release data of metformin.

RESULTS AND DISCUSSION

Preparation of two opposite charge polymeric complex of metformin HBS capsules

These HBS capsule of gastroretentive drug delivery showing great impact in recent days and specially those are absorbed in small intestine or in the stomach [16]. This capsule are floated due to the mixing the drug with colloidal gel-forming polymer that help to buoyant in the gastric content for long time. In past few decade there are several work reported by taking of chitosan in stomach-specific drug delivery due to its gel-forming nature as well as in stomach specific or gastroretentive HBS system [19, 23, 25]. Also, here I used xanthan gum as a very natural and economical polymer to reliability for compile with chitosan and produce more viscous to hydrate and float for release the drug for long periods of time [24, 26-28]. Also important things in my previous reported work formation of polyelectrolyte complex for sustain release drug delivery between two opposite charge polymer low molecular mass chitosan cationic nature and carboxy methyl tamarind gum anionic nature [16, 29, 30]. So in my current work similarly designing to opposite charge polymer MMMCH (Medium Molecular Mass Chitosan as a cationic) and XG (xanthan Gum as anionic) are taken to form electrolyte complex that could help to sustainliy release the drug metformin.

The HBS capsule of metformin will prepared by physical blending of drug metformin and two opposite charge hydrophilic polymer MMMCH and XG by adding other excipients like lactose, talc and magnesium state as diluents, glidant and lubricating agent and this blend were encapsulated in a single unit 000 size empty hard gelatin capsule. These hydrophilic natures of the two polymers will hydrocollodal gel when contact to dissolution medium and float for long periods of time and the opposite ionic nature of this polymer like cationic LMMCH and anionic XG will form an electrolyte complex between cationic MMMCH and anionic XG also help for sustain release of metformin from these HBS capsules.

Micromeritic propertie

The micromeritics properties of all formulations were showing in table 2. All the formulations depicted good flow ability by checking the parameters of CI in between 6.58 to 11.54, HR in between 1.07 to 1.13 and AOR in between 18.43 to 25.89. This is due to prevent the poor flow properties of the drug sample, and if we added the polymer with proper ratio and other excipients, that can help to improve the characteristic micropolitics properties of the formulation and developed the system.

Uniformity of weight

Table 3 will represent the value of weight uniformity of different capsules of metformin**.** All this formulation should follow the USP specification of weight uniformity test. Coefficient of variation to all formulation not more than 2.50 that's mean all formulation will be filled properly.

Uniformity of drug content

Drug content uniformity of all metformin capsules was shown in the table 4. The value ranges between 98.23±1.17 to 100.05±1.94 % that, confirms that the presence of metformin in sufficient quantity to all this formulation and passes this test.

Table 2: Micromeritics properties of different HBS capsules of metformin

Formulation code	BD in gm/cm³	TD in gm/cm³	CI in %	HR in degree	AOR in degree
MC1	0.638	0.683	6.58	1.070	18.432
MC2	0.588	0.642	8.41	1.095	21.389
MC3	0.555	0.604	8.11	1.088	22.678
MC4	0.518	0.578	10.38	1.115	24.567
MC5	0.498	0.563	11.54	1.130	25.890

n = 3, Hydrodynamically Balanced System (HBS)

Table 3: Weight uniformity test of different HBS capsules of metformin

Formulation code	Weight uniformity	
	mean weight (gm)±SD*	Coefficient of variation (%)
MC1	885.15±13.44	1.51
MC2	883.65±12.31	1.39
MC3	873.15±17.67	2.02
MC4	877.45±17.14	1.95
MC5	867.20±17.87	2.06

*SD = Standard deviation, n = 3, Hydrodynamically Balanced System (HBS)

Table 4: Result of drug content uniformity to all formulations

Formulation code	Drug content uniformity (%)
MC1	100.05±1.94
MC2	99.74±1.42
MC3	98.23±1.17
MC4	98.57±1.33
MC5	99.89±1.25

Data are given as mean±SD, n = 3

In vitro release of drug

The *in vitro* release of metformin from these capsules was analyzed in simulated gastric fluid (pH:-1.2) showing in fig. 1. Here all the formulation showing good *in vitro* drug release over a prolong periods of time that more than 12 h. All these HBS capsules of metformin represent well sustain release the drug that will prepare by 500 mg metformin and different ratio of LMMCH an XG. it is also notice that the *in vitro* sustain release of formulation will little bit increase when increase quantity of MMMCH by taking appropriate ratio containing XG that also reported in various previous work when this type of formulation make by taking of HPMC and Chitosan due to their ability for formation of hydro colloidal gel by contact with aqueous dissolution medium that enhanced the viscosity (23). Therefore, formulation MC4 (500 mg metformin with 100 mg MMMCH and 50 mg XG) showing better sustain release, although all the formulation perform similarly *in vitro* sustain drug release over a prolong periods of time (More than 12 h). Here another important things to the formation of an electrolyte complex by taking of two opposite charge polymers i. e. cationic MMMCH and anionic XG that also improved the sustain release the drug from different formulations.

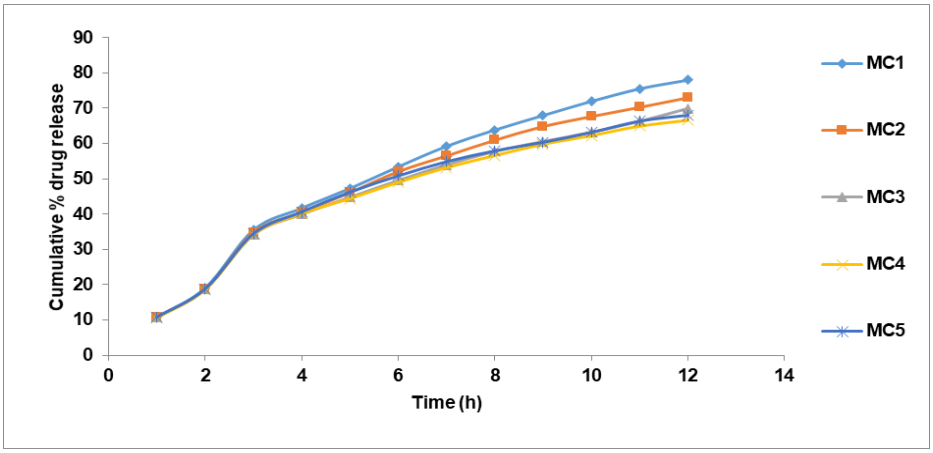

Fig. 1: *In vitro* release of metformin from the capsules. Error bars were omitted

In table 5 represent the different curve fitting mathametical kinetics model. All the formulation of metformin HBS capsule will fitted in Korsmeyer-Peppas model (R^2= 0.954 to 0.971). The release exponent (n) of all formulation was showing ranges within 0.72 to 0.78 refer to release mechanism like non-Fickian or anomalous diffusion indicating both controlled swelling and diffusion.

Table 5: *In vitro* release kinetics data of all formulation

Formulation code	R^2 Value					n value
	Zero order	First order	Higuchi	Korsmeyer-peppes	Hickson-crowell	
MC1	0.948	0.785	0.880	0.971	0.852	0.78
MC2	0.933	0.770	0.896	0.965	0.835	0.76
MC3	0.926	0.764	0.913	0.962	0.828	0.73
MC4	0.913	0.748	0.916	0.955	0.812	0.72
MC5	0.908	0.745	0.913	0.954	0.808	0.72

Fourier transforms infrared spectroscopy characterization

FTIR spectra of MMMCH (polymer), XG (polymer), metformin (drug) and the formulation MC4 (mixture of drug with polymer) for determine the polymer and drug-polymer interaction will be showing on fig. 2. The FTIR spectrum of polymer, polymer-polymer mixture and drug polymer mixture will show different characteristic peaks due to the stretching and bending of the presence of different functional group. This all type of peaks compare to the drug and formulation (MC4) that there will be no interaction as well as chemical or physical changes occur in between polymer-polymer and drug-polymer that maintain the stability.

Differential scanning calorimetric characterization

DSC thermogram of MMMCH (polymer), XG (polymer), metformin (drug) and MC4 (mixture of drug with polymer) for maintaining the stability will be showing in the fig. 3. The different endothermic peak of polymer, drug and drug polymer mixture (MC4) shows little bit shifting occur stability of the formulation.

In vitro floatation

For determination of *in vitro* flotation of these metformin HBS capsules, it was observed that formulation MC4 will floated in acidic medium (pH:-1.2) for more than 12 h without any floating lag time

(fig. 4). This type of flotation behaviors will study previously in some reported work [19, 21, 23], so this improved *in vitro* flotation due to colloidal hydrogel formation by presence of two hydrophilic polymers. This two hydrophilic polymers namely MMMCH and XG with the drug metformin was produced the polymeric drug matrix gel due to quick hydration of these polymer and swell to improving the viscosity. This matrix having great integrity to float the HBS capsules of metformin for prolong periods of time.

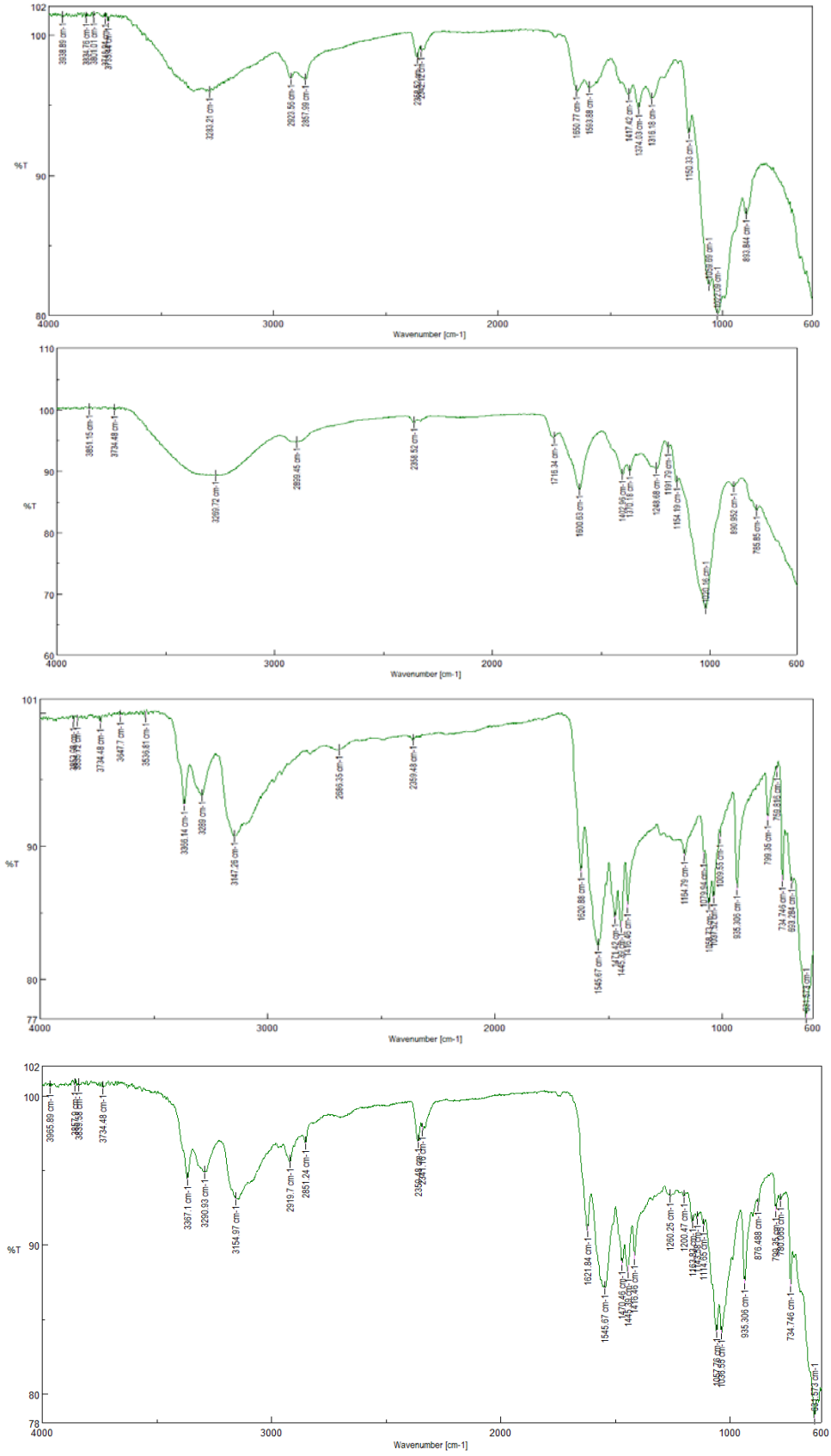

Fig. 2: FTIR spectra of MMMCH, XG, Metformin and MC4 HBS capsule

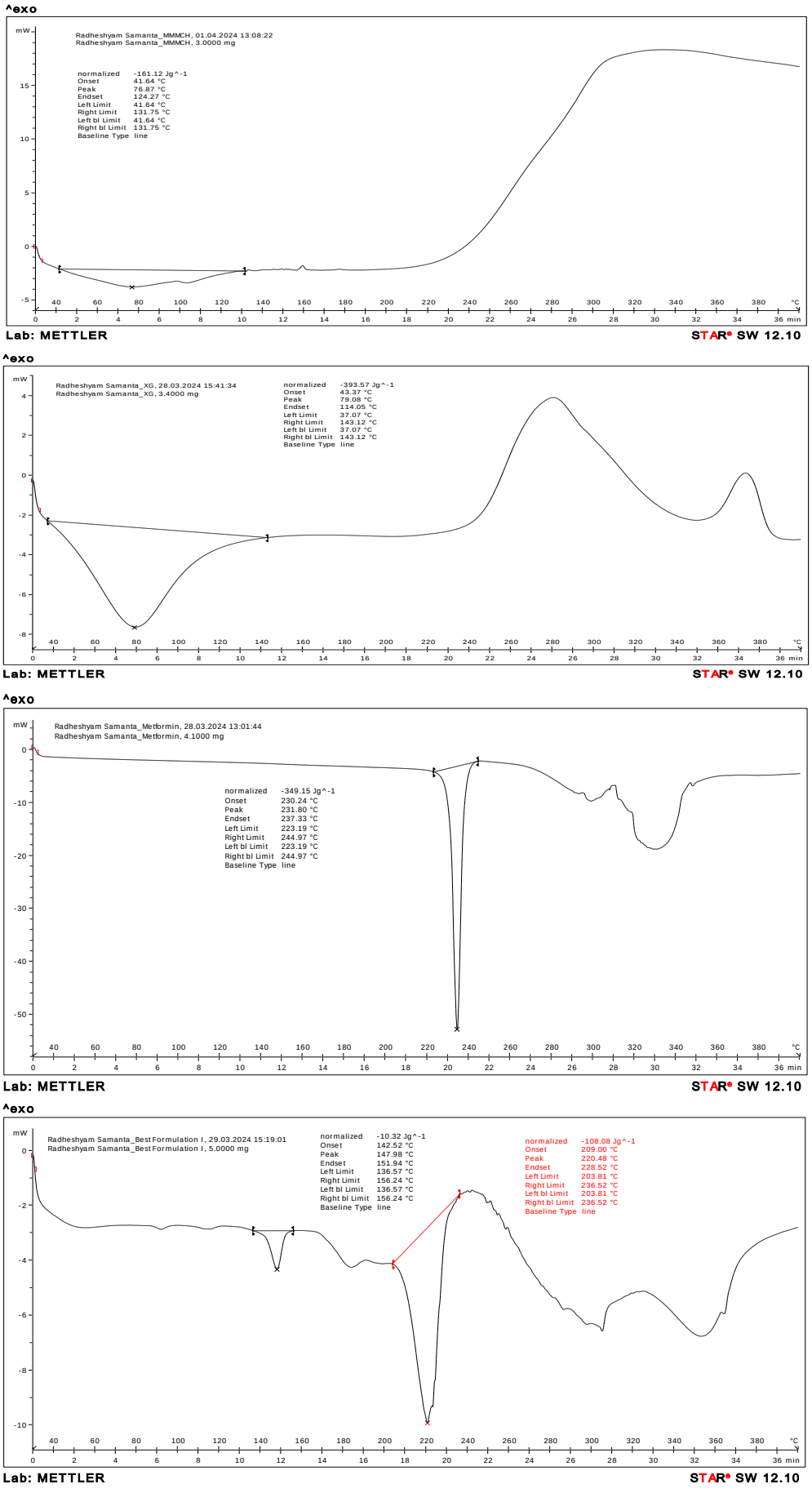

Fig. 3: DSC graph of MMMCH, XG, Metformin and MC4 HBS capsule

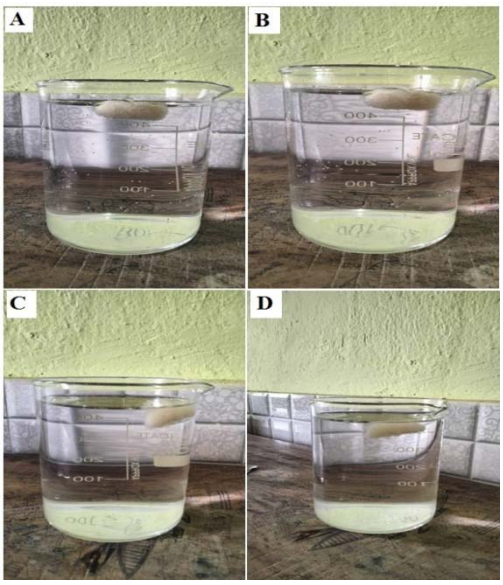

Fig. 4: *In vitro* floating behavior of metformin capsule

***In vivo* buoyancy through x ray radio photography**

For investigation of *in vivo* gastroretention of these metformin HBS capsules replace the drug metformin with barium sulfate by addition of MMMCH and XG to conducted X-ray radio photography by taking New Zealand adult male white rabbit [16, 29, 30]. The X-ray radio images of different time interval represented in fig. 5. It is clearly seen that the position of HBS capsules after oral administration in the gastric region or upper part of the intestine through X-ray images after 1h, 3h, 6h even 12 h of the oral administration as compare to before administration. However this study (x-ray images) clearly stated that *in vivo* gastroretention of these formulated HBS capsule in gastric region for a prolong periods of time will be demonstrated.

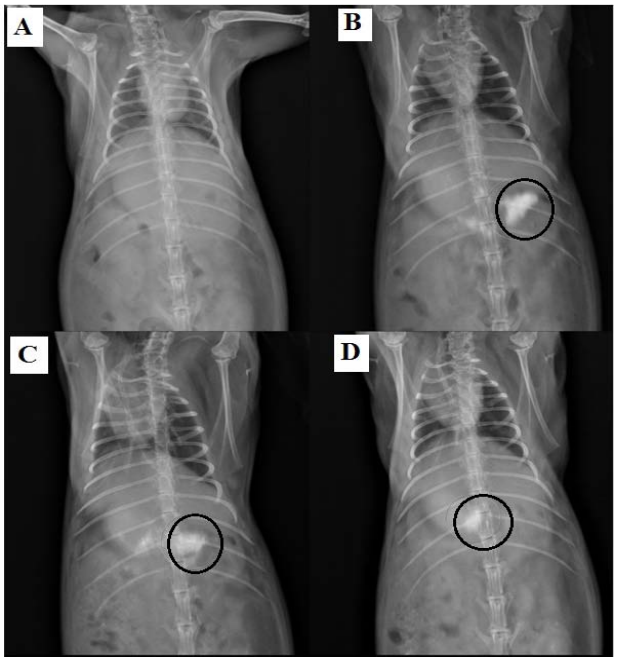

Fig. 5: *In vivo* X ray images of capsule in gastric region of rabbit

CONCLUSION

From this research work it was concluded that the formulation of stomach-specific HBS capsule of metformin prepared by physical blending of two opposite charge hydrophilic gel-forming colloidal polymer, namely cationic MMMCH and anionic XG (formation of electrolyte complex) help to sustain the release of drug. All these formulation showing great sustain drug release (*in vitro*) in gastric content (pH:-1.2) over more than 12 h, although the MC4 showing best sustain among this. Also *in vitro* buoyancy study showing all formulations specially MC4 will float more than 12 h in gastric content (pH:-1.2). In X-ray radio images of rabbit also demonstrated the (*in vivo*) gastroretention of floating HBS capsules for a prolong periods of time when administrated by replacing the drug with barium sulfate by addition of MMMCH and XG. So, these type HBS capsules of another drug with MMMCH and XG are also elegant for gastroretentive drug delivery system for their easy, negligible interaction, economical and sustain release for a prolong periods of time.

ACKNOWLEDGEMENT

The author would like to thanks all respected for guidance and help throughout this research work.

FUNDING

There is no funding to report

AUTHORS CONTRIBUTIONS

Investigation: Radheshyam Samanta, Gaurav Tiwari, Naveen Gupta, Dharmendra Singh Rajput. Methodology: Radheshyam Samanta, Gaurav Tiwari, Naveen Gupta, Dharmendra Singh Rajput. Supervision: Gaurav Tiwari, Naveen Gupta, Dharmendra Singh Rajput. Writing-original draft: Radheshyam Samanta. Writing-review and editing: Gaurav Tiwari, Naveen Gupta, Dharmendra Singh Rajput.

CONFLICT OF INTERESTS

The author declare that there is no conflict of interest

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