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ORIGINAL ARTICLE **OPEN ACCESS**

Preparation and Evaluation Of Sustained Release Tablets Of Highly Water Soluble Drug Metformin Hydrochloride

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ABSTRACT

The overall objective of this study was to develop an oral sustained release metformin hydrochloride tabletby using bigels of natural gums (gum acacia, locust bean gum and guar gum). The effect of diluents (lactose and calcium carbonate) on the drug release was also studied. All the formulations were evaluated for thickness, weight variation, hardness and drug content uniformity and in vitro drug release. From the results, it was clear that all the formulation shows uniformity among thickness, weight variation, hardness and drug content.SEM study of the granules was also undertaken to study the surface morphology of granules. The in vitro drug release data indicated that the release of drug from the system was sustained upto 6 h and hence confirms the drug release-retarding efficiency of the polymer. Kinetic modeling of in vitro dissolution profiles revealed the drug release mechanism ranges from diffusion controlled or Fickian transport to anomalous type or non-Fickian transport. Fitting the in vitro drug release data to Korsmeyer equation indicated that diffusion along with erosion could be the mechanism of drug release. It was observed from the results that all three gums employed in our study we reproved as suitable candidate for controlling drug release of highly water soluble drug by this mechanism. Drug release from Acacia gum was found to be more in compare to Locust beangum and Guar gum. The method of bigels preparation by emulsification method has been a novel approach in retarding drug release.

Keywords: *Bigels, sustained release, emulsification, natural gum*

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INTRODUCTION

A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body. This process includes the administration of the therapeutic product, the release of the active ingredients by the product, and the subsequent transport of the active ingredients across the biological membranes to the site of action. The term therapeutic substance also applies to an agent such as gene therapy that will induce in vivo production of the active therapeutic agent. Drug delivery system is an interface between the patient and the drug. It may be a formulation of the drug to administer it for a therapeutic purpose or a device used to deliver the drug. This distinction between the drug and the device is important, as it is the criterion for regulatory control of the delivery system by the drug or medicine control agency. If a device is introduced into the human body for purposes other than drug administration, such as therapeutic effect by a physical modality or a drug maybe incorporated into the device for preventing complications resulting from the device, it isregulated strictly as a device. There is a wide spectrum between drugs and devices, and the allocation to one or the other category is decided on a case by case basis. Sustained release (SR)preparations are not new but several new modifications are being introduced. They are alsoreferred to as "long acting" or "delayed release" when compared to "rapid" or "conventional" release preparations. The term sometimes overlaps with "controlled release," which implies more sophisticated control of release and not just confined to the time dimension [1].

MATERIAL AND METHODS

Metformin Hydrochloride was gift sample from OAPL Laboratories Himachal Pradesh. Guar gum, Locust bean gum, Gum acacia was procured from Sigma Aldrich, India. Calcium carbonates, Lactose, Magnesium stearate and Talc were purchased from CDH (New Delhi, India). All other chemicals were of analytical grade. Freshly distilled water was used throughout the work.

Quantitative estimation of drug

Preparation of calibration curve of metformin hydrochloride in 0.1M HCl (pH 1.2)

50 mg of drug was weighed accurately and dissolved in small quantity of 0.1N HCl (pH 1.2) in a 50 ml volumetric flask. Then the volume was made upto the mark using 0.1M HCl (pH 1.2).The above prepared solution of drug was subsequently diluted with 0.1M HCl of pH 1.2 to get 2, 4, 6, 8, 10µg/ml of the final solution. The absorbance of these solutions was measured at 231 nm against blank 0.1M HCl (pH 1.2) using UV spectrophotometer.

DSC characterization of drug

DSC study was carried out on pure drug. A weighed quantity of the sample was placed on the aluminium pans of the apparatus (PerkinElmer Pyris Diamond DSC) equipped with a Pyris – Instrument Managing Software, for computing the heat flow from the sample. Samples were heated at a scanning rate of 10°C over the range of 40°C to 300°C with 20 ml/min of nitrogen gas flow[2].

Drug excipient compatibility study

While designing any drug delivery system, it is imperative to give consideration to the compatibility of drug and polymer used within the system. Therefore it is necessary to confirm that drug is not interacting with polymers under experimental conditions and shelf life. The interaction studies can be done on the basis of Assay, UV, Infra red, DSC and TLC analysis.For the present study, the drug-polymer interaction studies were conducted by comparing it with the pure drug and physical mixture of drug-polymer by Infra red analysis and DSC[3].

Attenuated Total Reflectance-Fourier Transform Infrared Spectroscopy (ATR-FTIR) analysis

The pure drug, drug and mixture of it with the polymers were mixed separately with IR grade KBr in the ratio of 1:100 and corresponding pellets were prepared by applying pressure in a hydraulic press. The pellets were scanned over a wave number range of 4000 - 400 cm^{-1} in Fourier transform infrared spectrophotometer (JASCO FT/IR - 410). The liquid samples were analyzed by ATR[4].

Formulation Development

Preparation of the bigels

The bigels were prepared by fluid filled structure mechanism. The surfactant mixture of span 80: tween 80 (2:1 w/w) was used as the liquid gelator and was dissolved in 3.5 g of the olive oil at room-temperature (25ºC). To this solution of (50°C), 2.5 g of 1% (w/w) gum solution (gum acacia or guar gum or locust bean gum) in water (50°C) was added drop-wise with continuous stirring at 1000 rpm to form a homogenous emulsion. Thereafter, the emulsion (50°C) was cooled down to room-temperature to induce gelation [5].

Preparation of metformin hydrochloride burst release tablets

Sustained release tablets were prepared by wet granulation technique using a low density natural polymer i.e., guar gum or locust bean gum or gum acacia. The composition of the prepared tablets was shown in Table 1.The components were blended for 15 min, moistened with bigel binder to form a damp mass and wet granules were produced by passing through sieve no.12. The obtained wet granules were dried at 50ºC in hot air oven. Then the granules were passed through sieve no.16, with the lubricant talc and magnesium stearate, calcium carbonate or lactose, there by compressed on single punching machine.

Table 1:Composition of burst release highly water soluble tablet containing metformin hydrochloride with different release modifier polymers guar gum, locust bean gum and gum acacia.

Formulations	Composition for bigel (used as binder)						Composition of tablet					
	GG (mg)	LBG (mg)	AG (mg)	Span(ml)	Tween(ml)	Olive Oil(ml)	HPMC K4(mg)	Lactose(mg)	$CaCO_3$ (mg)	Metformin HCl(Mg)	Talc(mg)	MS (mg)
F1	20	…	…	2	1	1.5	100	100	…	650	10	30
F2	20	…	..	2	1	1.5	100	…	100	650	10	30
F3	…	20	…	2	1	1.5	100	100	…	650	10	30
F4	…	20	…	2	1	1.5	100	…	100	650	10	30
F5	…	…	20	2	1	1.5	100	100	…	650	10	30
F6	…	…	20	2	1	1.5	100	…	100	650	10	30

Evaluation of Prepared Tablets

Weight Variation

Twenty tablets were randomly selected and weighed individually and the weights of tablets were compared with the calculated mean weight. In this method, not more than two tablets should have a deviation greater than pharmacopoeia limits ± 5% of the weight.

Friability Test

Friability of the tablets was determined using friabilator. It subjected the tablets to the combined abrasion and shock in a plastic chamber revolving at 25 rpm for 4 minutes and dropping a tablet at height of 6 inches in each revolution. The tablets were reweighed. Tablets were de-dusted using a soft muslin cloth and reweighed. The percentage of the tablets friability was calculated as. The desirable friability was determined as lower than 1%[6].

Thickness

A vernier calliper was used to determine the thickness of randomly 10 selected tablets.

Hardness Test

The force required to break down a tablet in a compression is defined as the hardness or crushing strength of a tablet. In this study, ten tablets were randomly selected and individually placed in a Pfizer hardness tester and then the hardness of tablets reported in N.

Uniformity of content

Twenty tablets were accurately weighed and finely powdered. A quantity equivalent to 100 mg of drug was transferred to a 200 ml volumetric flask. To it, 50 ml of 0.1M HCl was added and shaken to dissolve drug. Resulting solution is diluted to volume with 0.1M HCl and filtered. 20 ml of filtrate diluted to 100ml with 0.1M HCl and mixed. Absorbance of the resulting solution at maximum at about 231 nm was measured UV spectrophotometer (Shimadzu) [7].

Scanning Electron Microscopy (SEM) study

The surface morphologies of the prepared granules were investigated by using Scanning Electron Microscope (SEM, model no. Supra 40 VP), Zeiss, Germany. Prior to examination, samples were gold coated (thickness 12-15 mm) has been deposited using Emitech to make them electrically conductive.

***In Vitro* dissolution studies**

The *In vitro* dissolution study was performed by using a USP XXII paddle apparatus at a rotational speed of 50 rpm. Exactly 900 ml of 0.1 M HCl was used as the dissolution medium and was maintained at 37±1°C. Then, 5 ml of the dissolution medium was withdrawn at specified time interval until 6 h. Exact 5 ml of fresh medium was replaced to the dissolution vessel after each withdrawal to maintain a constant volume. The samples withdrawn were analyzed by using a UV spectrophotometer (Shimazdu, Mumbai, India) at 231 nm[8].

Drug release kinetic study

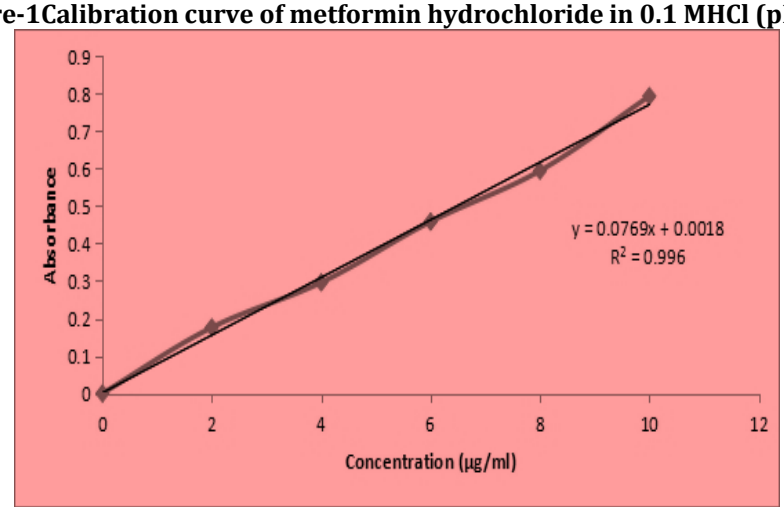
The rate and the mechanism of release of metformin hydrochloride through the prepared formulations were analyzed by fitting the drug released data into zero order (percentage of drug released vs. time), first order (log percentage of drug to be released vs. time), Higuchi's (percentage of drug released vs. square root of time) and Korsmeyer Peppas (percentage of drug released vs time)

RESULTS AND DISCUSSION

Quantitative estimation of drug

The absorption maxima of drug solution (10µg/ml), as determined by UV-Spectrophotometry was found to be 231 nm in 1.2 pH 0.1MHCl when scanned between 400 - 200 nm. The method of analysis using UV Spectrophotometry of metformin hydrochloride at a scanned wavelength range was found to be reproducible. Standard calibration curve of drug was prepared in 0.1MHCl pH 1.2 at 231 nm, using UV/Visible spectrophotometer. The standard curve is shown in Fig.1 [9].

Figure-1Calibration curve of metformin hydrochloride in 0.1 MHCl (pH 1.2)



The absorbance data presented in Table 1 were found to obey Beer's law within the specified range as indicated by the statistical analysis undertaken. The observations are presented in Table 2. The data were found to have nearly perfect correlation coefficient 0.996 and hence it is linear in nature. The reproducibility of the method was tested by repeating the procedure.

Table 2: Calibration data of metformin hydrochloride in 0.1 MHCl (pH 1.2)

S. No.	Concentration (µg/ml)	Absorbance
1.	0	0
2.	2	0.176
3.	4	0.296
4.	6	0.458
5.	8	0.594
6.	10	0.793

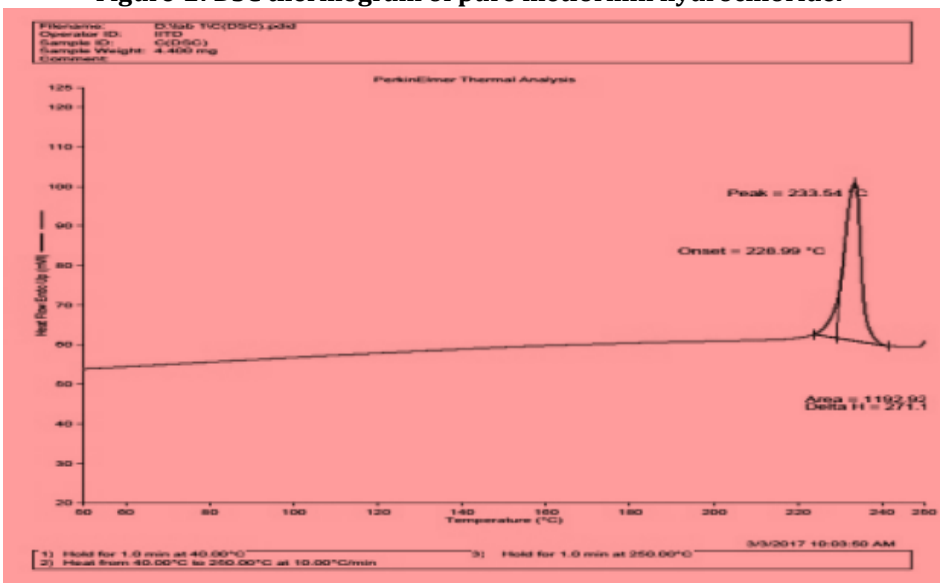
Table 3:Statistical parameter related to standard curve

S. No.	Parameters	Values
1.	Regression coefficient	0.996
2.	Intercept on y-axis	0.001
3.	Equation on line	y = 0.076x + 0.001

DSC study of drug

The DSC thermogram of pure metformin hydrochloride showed endothermic peak at 233.54ºC was attributed to its melting point.

Figure-2: DSC thermogram of pure metformin hydrochloride.



Drug Excipient Compatibility Studies

The ATR spectra of pure gums were represented in Fig. In the ATR spectra of Acacia gum (Fig.3 (a)), a characteristic absorption band at 3371.57 cm^{-1} representing the presence of hydrogen bonded OH group was observed. The characteristic absorption band in the region 3371.57 cm^{-1} for amino group must have been masked by the broad OH group absorption band. The bands at 2924.09 cm^{-1} indicate the presence of sugars, also the presence of alkane C-H stretch and aldehyde C-H stretch. The polymers also showed the characteristic band of C=C stretch, amide NH bend, NO_2 from both aliphatic and aromatic galactoproteins, and amino acids around 1654.92 cm^{-1}. The glucuronic acids have specific vibrations such as the band at 1468.18 and 1364.03 cm^{-1} due to C=O symmetric stretching and -OH bending, respectively. A distinct band at around 1099 cm^{-1} represents alkene CH bend from polysaccharides [10].The ATR spectrum of Guar gum (Fig. 3(b)) exhibits the characteristic absorption band at 3348.2 $cm^{-1}$and 2931 cm^{-1}due toO-H stretching vibrations of the polymer associated with C-H stretching vibrations. Additional information from the characteristic absorption bands of GG appears at 1458.18 cm^{-1} and 1165 cm^{-1}due to C-H bending and O-H bending vibrations [11].For pure locust bean gum (Fig. 3 (c)), the band at 3352.28 cm^{-1}represents O–H stretching vibration. The band at 2927.94 $cm^{-1}$is due to C–H stretching of the $–CH_2$ groups. The bands dueto ring stretching of galactose and mannose appear at 1651.07 cm^{-1}. In addition, the bands in the region of 1354.03 and 1462.04 cm^{-1} are due to symmetrical deformations of CH_2 andCOH groups. The bands due to primary alcoholic $–CH_2OH$stretching mode and CH_2 twisting vibrations appear at 1111.0 cm^{-1}. The weaker bands around 721.38 $cm^{-1}$are due to ring stretching and ring deformation of α-D-(1-4)and α-D-(1-6) linkages [12].The ATR spectra of mixture of drug with polymers (gum) were shown in Fig. 4, Fig. 4(a) represents ATR spectra of drug with acacia gum, Fig. 4 (b) spectra of drug with guar gum while Fig. 4(c) represents spectra of drug with locust bean gum. All the spectra of the combination confirm the compatibility of the drug with gums as the characteristic peak of drug (NH stretching at about 3372.03 cm^{-1} remains intact in all the combination (Fig. 5).

Figure-3: ATR spectra of pure gums. (a) Acacia gum; (b) Guar gum; (c) Locust bean gum

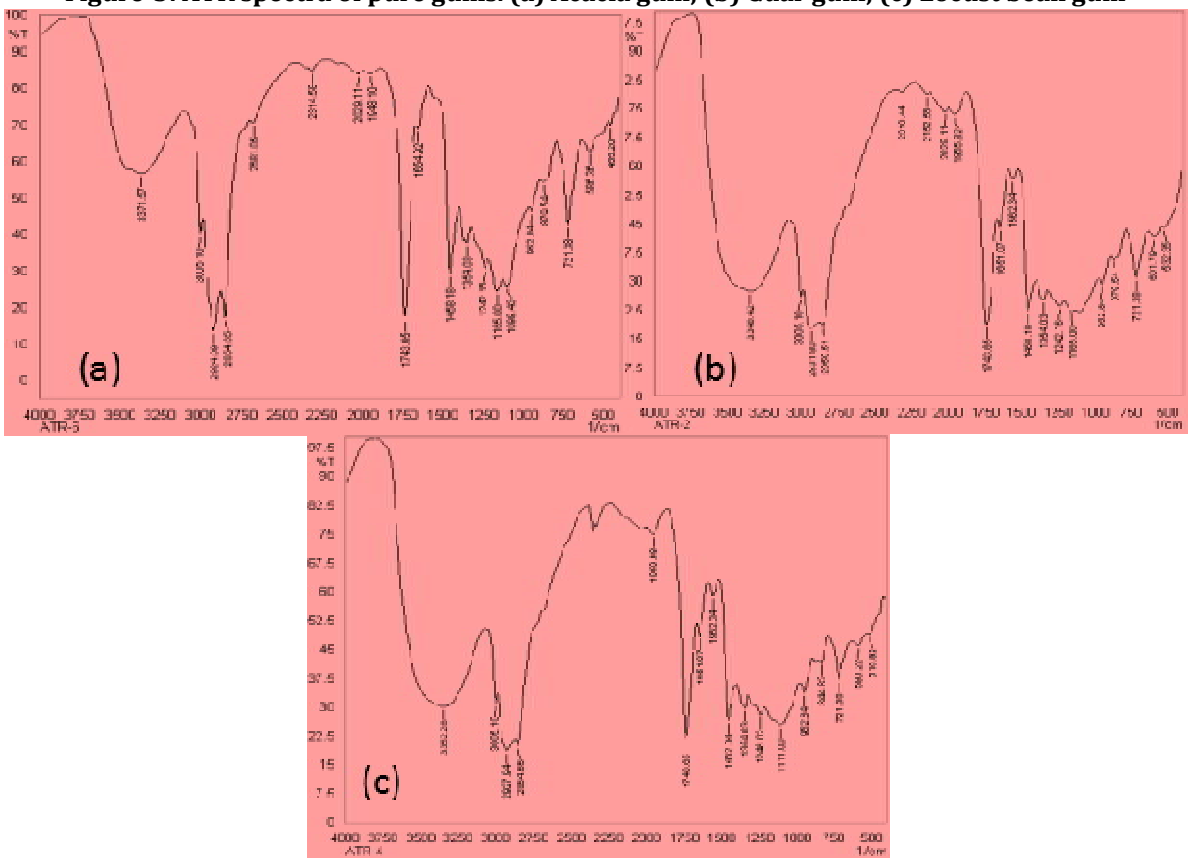


Figure-4: ATR spectra of physical mixture of drug with various gums. (a) Drug with Acacia gum; (b) Drug with Guar gum; (c) Drug with Locust bean gum.

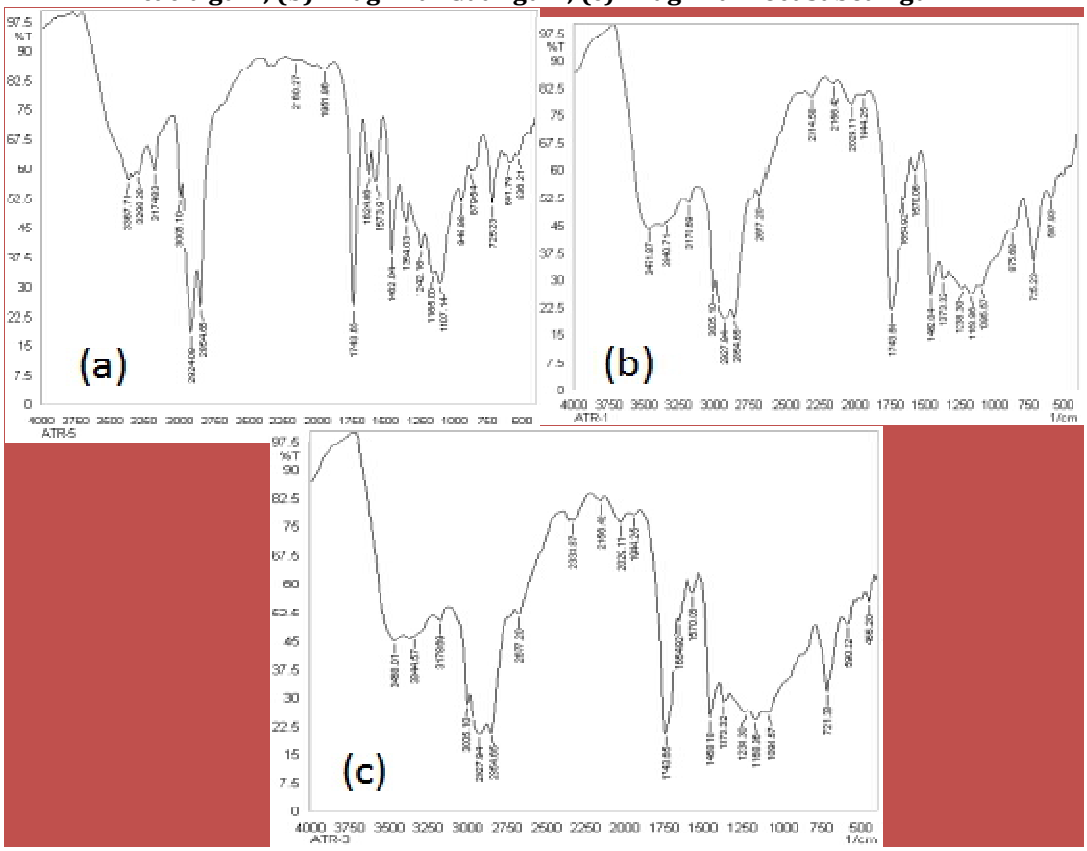
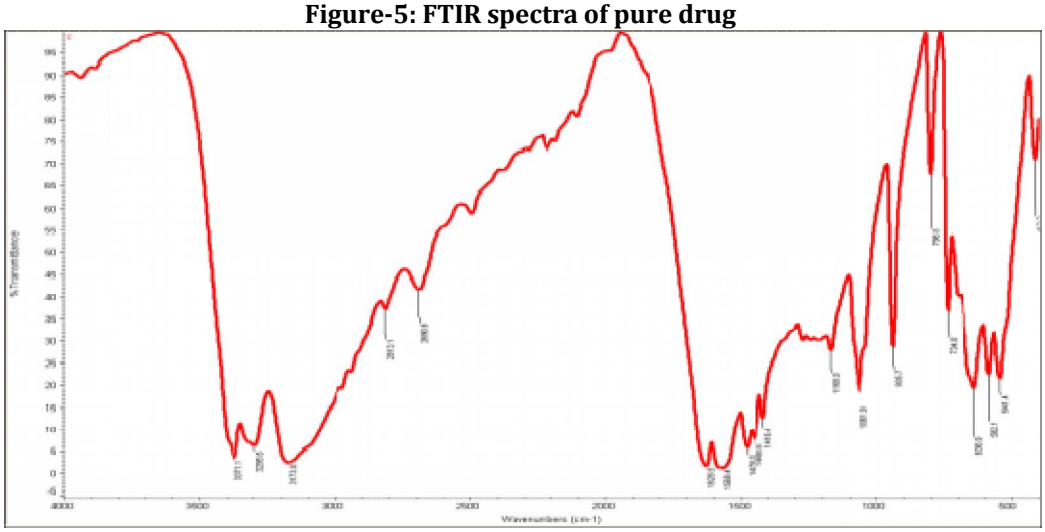


Figure-5: FTIR spectra of pure drug



Preparation of Bigels

The homogenized solution of S mix in oil was transparent and pale brown in color. The addition of the gum solution to the Smix solution resulted in the formation of white mixture, indicating the formation of an emulsion. The bigels appeared as milky-white due to the diffraction of the light from the interface of the polar and the polar phases. The formulations formed were smooth to touch and gave a cooling sensation, when a thin smear was applied over the skin surface. There was no gritty feeling (often associated with the formulations made with solid gelator molecules) or odor.

Evaluation of Prepared formulations

Physicochemical evaluation of tablets

The prepared tablets were off-white, smooth, and flat shaped in appearance. The results of physicochemical characterizations are shown in Table 4. Tablets were exposed to all of the physicochemical tests. The weight of formulated tablets met the pharmacopoeia criteria. Physicochemical

tests were conducted on complete tablets including assay, hardness, friability, thickness, weight variation (Table 4). All tablets had similar conditions in the weight variation test in pharmacopoeia limits i.e. ± 5%. The drug content of the whole formulations was put down in the range of 99.3-100.2%. Friability of the all formulations was found to be lower than 1%. The hardness of the tablets was measured by Pfizer tester (Indian Equipment Corporation Mumbai, India) and was controlled between 4.5±0.05and 7.2±0.06kg/cm^2. The thickness of tablets was measured by Vernier Caliper and was ranged between 7.51 to 8.3mm.

Table 4:Physicochemical characterization of prepared tablets of metformin hydrochloride.

Formulation code	Hardness Kg/cm^2	Thickness (mm)	Friability (%)	Weight Variation (%)	Drug content (mg/tablet)	Assay (%)
F1	4.8±0.02	8.3±0.07	0.57	809±1.3	651±2.1	100.2±1.53
F2	6.7±0.07	7.59±0.09	0.49	806±2.1	648±2.6	99.9±1.04
F3	4.5±0.05	7.96±0.08	0.63	825±1.1	649±3.9	99.7±1.75
F4	6.2±0.06	7.9±0.19	0.76	806±2.4	647±4.6	99.4±1.23
F5	7.2±0.06	7.51±0.19	0.57	807±3.9	645±6.4	99.8±1.92
F6	4.7±0.04	8.13±0.06	0.94	827±2.6	651±4.3	99.3±1.19

Scanning Electron Microscopy

Scanning electron microscopy (SEM) is a commonly used technique to examine the surface morphology of tablets and to visually support other qualitative and quantitative results [13]. The SEM study was carried out for formulated granules of three gums (viz gum acacia, guar gum and locust bean gum)t to check the surface texture of the same. The Fig. 6.6, 6.7 and 6.8 and showed the micrographs of the granules prepared by guar gum, locust bean gum and gum acacia, respectively at different magnifications. The images of the granules showed a network in the swollen polymer through which the drug could be diffused to the surrounding medium.

Figure- 6: SEM micrographs of granules prepared by using guar gum. (a)at 100X, (b) at 1000X, (c) at 2000X

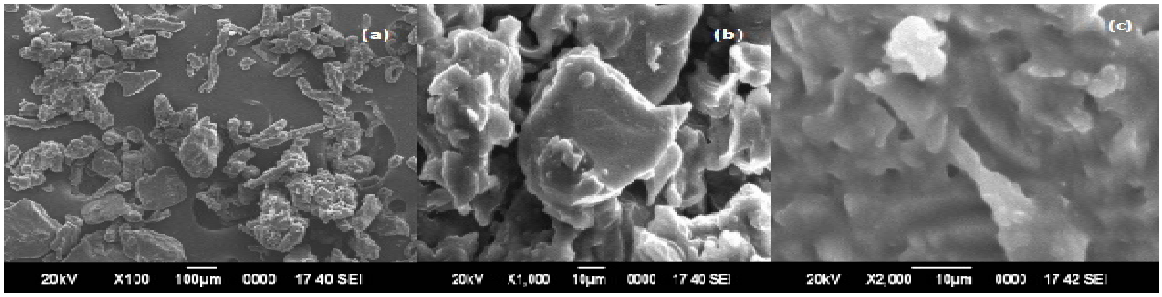


Figure-7: SEM micrographs of granules prepared by using locust bean gum. (a)at 100X, (b) at 1000X, (c) at 2000X

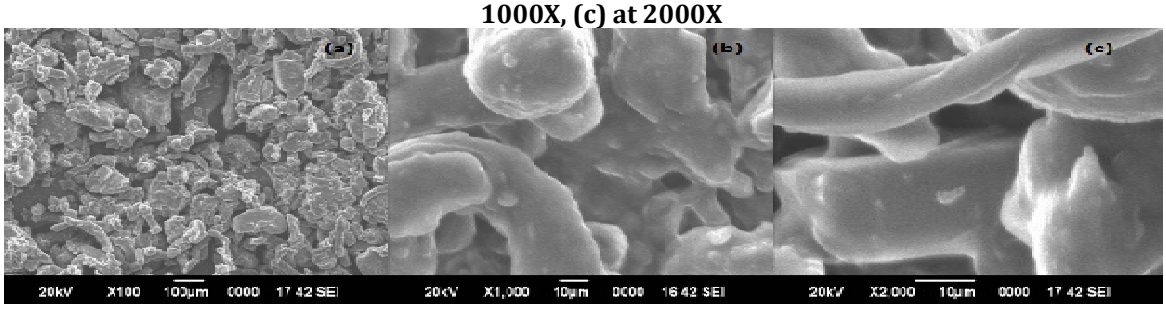
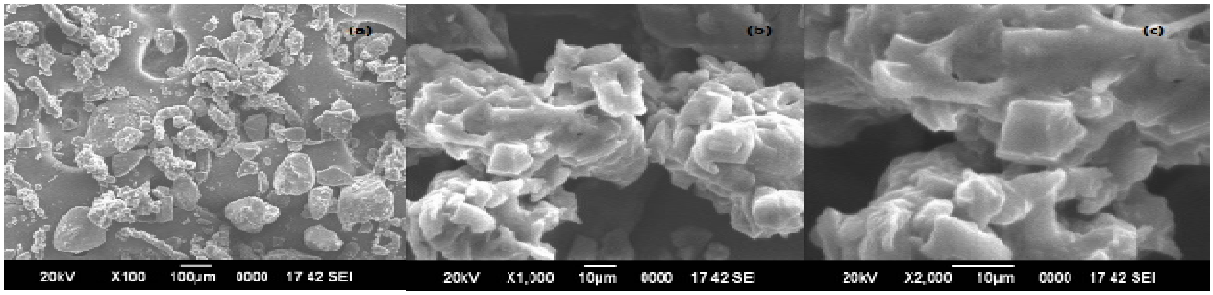


Figure-8: SEM micrographs of granules prepared by using guar gum. (a)at 100X, (b) at 1000X, (c) at 2000X



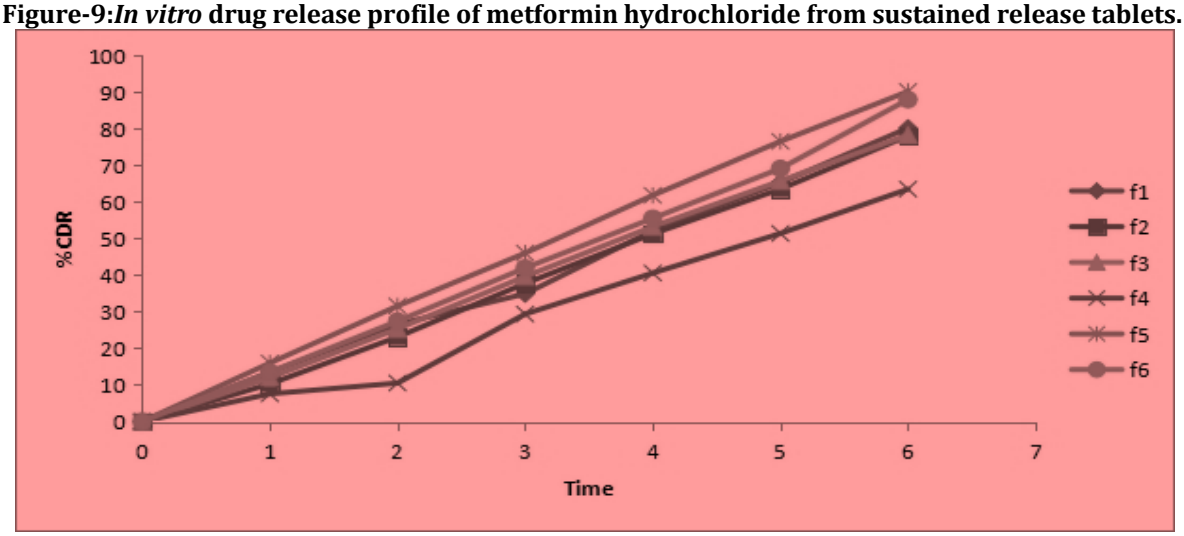
In vitro drug release

The rate of dissolution determines the rate and extent of absorption and subsequent therapeutic outcome of a drug. The factors that affect dissolution include type and concentration of polymer and excipient. In vitro dissolution studies of all the formulations of sustained release tablets of metformin were carried out in 0.1 M HCl. The study was performed for 6 h, and cumulative drug release was calculated at 1-h time intervals. The drug release was sustained up to 6 h duration of the study and ranges from 63.48 to 90.17 %. Figure 6.8 and Table 6.4 summarize the % drug release from all the formulated of tablets. At the end of 6 h, the percentage drug release from the formulation F1, F2, F3, F4, F5, F6 was found to be 80.17± 2.55%, 78.03±2.06%, 78.29±2.54%, 63.48±2.08%, 90.17±3.24%,87.98±2.33% respectively.

Table 5:Cumulative % Drug release from sustained release tablets of metformin hydrochloride

Time (h)	Percentage cumulative drug release					
	F1	F2	F3	F4	F5	F6
0	0	0	0.	0	0	0
1	13.45±0.89	10.27±0.63	11.98±0.87	7.56±0.57	15.98±0.65	13.05±0.87
2	26.56±1.23	23.09±1.11	25.31±2.01	10.56±1.15	31.56±1.64	27.42±1.32
3	34.86±0.98	37.72±1.63	37.63±1.99	29.35±1.98	46.02±2.16	41.95±1.57
4	52.13±2.31	51.27±2.5	53.25±1.54	40.56±2.18	61.78±2.65	55.51±2.14
5	65.23±1.78	63.51±2.98	65.72±2.33	51.37±2.34	76.52±2.98	69.12±2.36
6	80.17±2.55	78.03±2.06	78.29±2.54	63.48±2.08	90.17±3.24	87.98±2.33

Figure-9:*In vitro* drug release profile of metformin hydrochloride from sustained release tablets.



In the present investigation two types of tablet diluents were used viz. Lactose (F1, F3 & F3) and Calcium carbonate (F2, F4 & F6). Although it was not the focus of the study, but the difference in release profile of metformin HCl from sustained release tablets prepared with calcium carbonate and lactose prompted us to look into the matter and deduce possible explanation for this observed behavior. In general drug release from sustained release tablets containing lactose was significantly faster than tablets containing the calcium carbonate as diluents. As a general rule, polymer dissolution and erosion take place in three steps: Solvent penetration into the polymer matrix, polymer swelling and chain disentanglement and attainment of the threshold disentanglement. When dissolution medium penetrates into the polymer matrix, it enhances the mobility of the polymer chains which eventually disentangle at the advancing front, separating the gel layer from the erosion/dissolution front. Here, presence of lactose might have enhanced osmotic pressure, which accelerates dissolution medium penetration into the matrix resulting in a higher degree of polymer swelling and formation of more micro-cavities, therefore, higher release rates compared to formulations containing calcium carbonate. The addition of HPMCwas fixed in all formulation to increase strength of bigel due to its greater swelling which could resulted in increase in diffusion path length leading to retarded diffusion of metformin HCl through the swollen hydrogel[14].

Drug Release Kinetics

The in vitro release pattern of various formulations was analyzed by fitting the dissolution data into various kinetic models (table 5). The R^2 values of all the formulation (F1 to F6), were found higher when fitted to a zero-order equation, which indicated a zero-order release from these formulations. This indicates drug release is independent of metformin concentration in the formulation. Formulation F1 and

F5 followed the case II transport mechanism which suggests that the dominant mechanism for drug transport is due to polymer relaxation as the gels swells. On the other hand, formulations F2, F3, F4 and F6 followed the super case II transport mechanism, which is characterized by acceleration in solvent penetration into the polymer matrix. The speed of solvent diffusion in the matrix is much greater than the swelling, with this being the determining factor in the drug release. It was observed from the results that all three gums employed in our study were proved as suitable candidate for controlling drug release of highly water soluble drug by this mechanism. Drug release from Acacia gum was found to be more in compare to Locust bean gum and Guar gum. The method of bigels preparation by emulsification method has been a novel approach in retarding drug release[15].

Table 6: Kinetic modeling of the prepared formulations.

Formulation Code	Zero order	First order	Higuchi	Kosmeyer Peppas	
	R^2	R^2	R^2	R^2	N
F1	0.995	0.928	0.895	0.993	0.990
F2	0.998	0.945	0.891	0.999	1.133
F3	0.999	0.958	0.908	0.999	1.053
F4	0.978	0.950	0.836	0.947	1.284
F5	0.999	0.912	0.921	0.998	0.998
F6	0.997	0.882	0.897	0.993	1.069

CONCLUSION

Sustained-release (SR) oral delivery systems are designed to achieve therapeutically effective concentrations of drug in systemic circulation over an extended period of time. Possible therapeutic benefits of a properly designed SR dosage form include low cost, simple processing, improved efficacy, reduced adverse events, flexibility in terms of the range of release profiles attainable, increased convenience and patient compliance. Sustained release products are needed for metformin to prolong its duration of action and to improve patient compliances. The present study showed the potential use of bigels of the natural gums/polymers to control the release of the drug from the system. The findings of the present study demonstrate that all three gums employed in our study were proved as suitable candidate for controlling drug release of highly water-soluble drug by this mechanism and can therefore be successfully employed for formulating sustained release matrix tablets. Diffusion coupled with erosion might be the mechanism for the drug release, which can be expected to reduce the frequency of administration and decrease the dose-dependent side-effects associated with repeated administration of conventional metformin HCl tablets. Moreover, drug release from acacia gum was found to be more in comparison to Locust bean gum and Guar gum. Therefore, it is clear that the use of bigels of gums instead of pure gum can prove to be a novel approach in retarding drug release.

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