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FORMULATION AND EVALUATION OF SUSTAINED RELEASE TABLET OF HIGHLY WATER SOLUBLE ANTI-DIABETIC DRUG METFORMIN HCL

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ABSTRACT

The current study demonstrated how bigels of natural gums and polymers (Chitosan with Karaya gum, locust bean gum, and Guar gum) might be used to regulate the drug's release from the body. The results of this study show that all three of the gums used in our investigation were shown to be good candidates for regulating the release of highly water-soluble drugs through this mechanism. As a result, they can be effectively used to formulate sustained release matrix tablets. By using diffusion in conjunction with an erosion mechanism, this delivery system aims to lower the frequency of administration. Furthermore, it was discovered that CH-Karaya gum released more drugs than Guar and Locust bean gum. Consequently, it is evident that using bigels of gum rather than pure gum can be a novel way to delay the release of drugs.

KEYWORDS: Chitosan, guar gum, karaya gum, locust bean gum, metformin HCL, natural gums, sustained release.

INTRODUCTION

Novel Drug Delivery System (NDDS)

Chien (2007), Drug distribution is accomplished by a number of sophisticated methods. The methods were primarily utilised to target a specific tissue, extend the duration of effect, and regulate the rate of drug delivery. These developments have led to the development of several

NDDS systems with a variety of therapeutic advantages.

Reduction of negative side effects maximising the connection between efficacy and dose. Improvement of patient compliance decreased frequency of dose. An ideal concentration can sustain the extended duration of treatment.

Sustained Release System

These are the prolonged type systems, which increase the release time while releasing the medication very slowly.

(a) Controlled Release (CR): Releases medication at a specific rate both locally and systemically.

(b) Prolonged Release (PR): Lengthens the duration of action and keeps the medication level in the blood or target tissue constant.

Sustained Release Drug Delivery System (SRDDS)

In order to achieve a therapeutic result, a number of innovative drug delivery systems have been developed that tend to increase the drug's effectiveness and consequently regulate its release within the body by affecting its speed, length, and release mechanism. The active chemicals are released and transported to the place of action.

According to **Sampanth *et al*., 2012,** the development of SRDDS has become more important in the current era in order to maintain a steady medication (as opposed to "rapid" or "conventional" release preparations), are designed to modify or improve the drug action by increasing the duration of action, decreasing the frequency of dosing, reducing side effects, and lowering the required dose (Fig1).

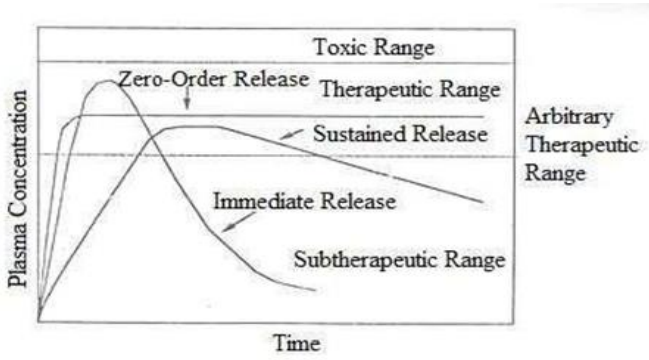

Fig. 1: Profiles of Plasma Drug Concentration (Patel *et al*, 2004).

Justification for a Drug Delivery System with Controlled/Sustained Release

There are a number of ways to improve drug releases, including: coating drugs with polymers

to create laminates; dispersing drugs adding drugs to bioadhesive polymers that can stick to mucous membranes to release drugs for extended periods of time; and chemically bonding drugs with polymers (amide or ester linkages) to control drug release. Making a laminate by applying a polymer covering; Hydrogel is produced in a matrix by drug dispersion; Pellets or micropellets for slow and extended drug release can be made by coating drugs; drug addition to a bioadhesive polymer that has the ability to adhere to mucosal membranes and deliver medication gradually; using polymers (ester or amide bonds) to chemically bind drugs in order to control drug release.

Sustained Release Benefits

Sampanth *et al*., 2012, Easier control over drug absorption; less variation in blood levels; support for bioavailability, fewer side effects, and drug accumulation; By offering large safety margins, side effects can be minimized; Enhanced bioavailability and therapeutic outcome; economically advantageous.

Sustained Release Drawbacks

High cost; decreased systemic availability (compared to rapid release dosage forms); higher potential for first pass metabolism; diminished potential for dose modification; need for patient counselling; weak *in vitro* and *in vivo* correlations.

Burst Release

According to **Huang *et al*., 2001,** a number of studies have identified the mechanism of burst and incorporated burst into a model to mimic the release, which has been used as part of the drug administration strategy to give the medication at a high release rate (Fig.2).

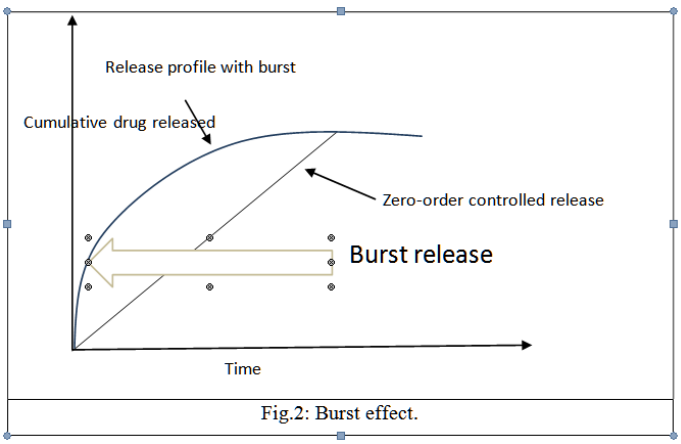

Fig.2: Burst effect.

It has been investigated in most published result and been ignored in most mathematical

models. However, among the plethora of controlled release publication, burst phenomena have been observed and studied. Several researches have observed burst release without giving advanced explanation; some tried to find the mechanism of burst and prevent technology; and some have made an effort to include burst in model to simulate the release has been utilized to deliver drug at high release rate as part of the drug administration strategy.

The development of a monolithic matrix formulation for highly water-soluble drugs has been an interesting topic of research compared to the membrane coated systems. However, problems have been encountered for matrix systems for the oral controlled release delivery of freely water-soluble drugs dose dumping, the burst phenomenon, and difficulty in achieving 24-hour linear release profile. Recently, a new approach for *in situ* interactions between drug and electrolyte(s)has been designed to control the release of highly water-soluble drugs from oral hydrophilic monolithic systems, in which the model drug diltiazem hydrochloride in conjunction with sodium bicarbonate and hydroxyl propyl methylcellulose drug metoprolol tartrate in combination with sodium carbonate and poly(ethylene oxide) (PEO) have respectively achieved a 24-hour release profile in a zero-order manner in a different pH environment. Sodium alginate and xanthan gum are natural polymers, both of which have been employed as matrices for prolonged drug delivery systems Sodium alginate is a water-soluble salt of alginic acid, a naturally occurring, nontoxic polysaccharide found in all species of brown algae. Sodium alginate contains two uronic acids, b-D-mannuronic acid (M) and a-L guluronic acid (G), and is composed of homo polymeric blocks MM or GG, and blocks with an alternating sequence, the MG blocks. It can form hydrophilic gels by interacting with many divalent cations except magnesium. Gelation occurs by cross-linking of the uronic acid units with divalent cations. Crosslinking by calcium occurs primarily with the GG blocks to form the so-called, "egg-box'' structure. However, it has been suggested that cross-linking with zinc may occur in the MM and MG blocks as well

The Challenges with highly water-soluble drug for development of oral modified drug delivery systems are as follows

- The major challenge experienced by pharmaceutical technologist includes the development of oral controlled release tablets for highly water-soluble drugs with enhanced controlled release rates. The drug could be released at a faster rate than desired and can cause toxicity on oral administration in case of highly water-soluble drugs.

Therefore, to formulate a suitable tablet dosage form for extended delivery of highly water-soluble drugs is a challenging task.

- If the drug of a high water-solubility is also of a short half-life (i.e., quickly metabolized in the body thereby losing its activity), the drug would remain in the blood for only a short time, resulting in a short duration of action.

- For such a drug, a multiple daily dosing regimen (three, four or more times a day) is necessary to maintain a steady drug concentration in the blood above its effective concentration level. A multiple daily dosing is inconvenient and reduces the patient compliance significantly.

Consequently, when doses are not administered on schedule, the resulting" peak and valley" effect in the blood concentration reflect less than an effective drug therapy. Considering all these problems associated with conventional dosage forms, there is critical need of development of modified release dosage forms for highly water-soluble drugs which can overcome the drawbacks associated with existing approaches and market products of highly water-soluble drugs.

Metformin hydrochloride (N,N-dimethylimidodicarbonimidicdiamide hydrochloride) is a member of the biguanide class of oral antihyperglycemic drugs. This drug is designed for a once-day oral administration using polymers based on polyelectrolyte complexation technology. SRDDS of metformin was developed to attempt sustained release formulation. Present work was undertaken to develop sustained formulation for prolonged duration bearing frequent dosing and improving patient compliance. In recent years, significant efforts have been made to develop various drug delivery system, of which one is the sustained drug delivery system.

This system primarily explores various polymers that could be used as a carrier to enhance the sustained release of the drug at the specific site for a better therapeutic outcome. One such polymer that is used in this study is Chitosan and its relatively known to act as a carrier supporting the main drug of action for its sustained release. This polymer is considered to be a potent carrier due to its mucoadhesive property.

That enables it to form hydrogen bonds with the mucus membrane. Apart from that it also exhibits cell-binding property due to its cationic polyelectrolyte structure.

MATERIALS AND METHODS

The present study is focused on development of a suitable formulation for sustained release and specific drug delivery against type-2 diabetes by forming a bigel using polymers of different charges to release highly water soluble durg Metformin HCl (Fig.3) with the following objectives: to increase the medicine metformin's bioavailability by creating a bigel with the help of appropriate polymers; to carry out an in vitro bioavailability research and assess the drug's improved bioavailability. to create a stable tablet or formulation and assess its stability in accordance with ICH standards.

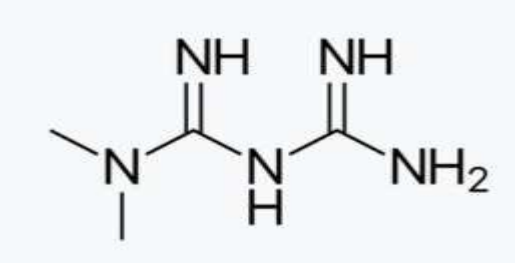

Fig. 3: Metformin Chemical Structure.

Description of Metformin

- IUPAC Name : N,N-Dimethylinidodicarbonimidic diamide
- Synonyms : N, N – dimethylbiguanide
- White to off-white crystalline in colour
- Readily soluble in water and insoluble in acetone, ether, and chloroform
- Chemical Formula : $C_4H_{11}N_5$; Molecular Weight-129.167 g/mol

Mechanism of Action

- Metformin improves glucose tolerance in type 2 diabetes (lowering both basal and postprandial plasma glucose);
- Shows different set of pharmacological mechanism of action;
- It decreases hepatic glucose production, and decrease absorption of glucose;
- Does not produce hypoglycemia (even in normal subjects); does not cause hyper-insulinemia;
- Insulin secretion remain unchanged with metformin;
- It causes a decline in the insulin levels and day long plasma insulin response.

Pharmacokinetics

The 850mg showed an apparent volume of distribution (V/F) 654 ± 358 L. Metformin

90% bounded to proteins. Drug is excreted unaffected in the urine. Within the first 24 hours roughly 90% of the drug absorbed gets eliminated via the renal route. Used as monotherapy to improve glycemic control in patients with type-2 diabetes. Contraindications include cardiovascular collapse, acute myocardial infarction, Septicemia, congestive heart failure (CHF), hypersensitivity.

Determination of Absorption Maxima

A UV absorption maxima was determined by scanning a 10 µg/ml solution of Metformin Hydrochloride in 0.1M HCl pH 1.2 between 400nm - 200nm.

Preparation of Standard Curve

Preparation of 0.1M HCl pH 1.2: 8.5 ml of hydrochloric acid was dissolved in small amount of distilled water and finally the volume was made up to 1000 ml with distilled water (pH was adjusted if necessary using either base or acid).

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 up-to 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 absorbances of these solutions were measured at 232 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.

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.

Fourier Transform Infrared Spectroscopy (FTIR) analysis

The pure 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 (Shinatzu 8400).

Formulation Development

The bigels were prepared by fluid filled structure mechanism. The surfactant mixture of tween 80: Span 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 (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.[63]

Preparation of Metformin Hydrochloride burst release Tablets

Preparation of Bigel layer

The binders are used to hold together the structure of the tablets. When sufficient compression forces are applied they bind other ingredients together and thereby contribute to the integrity of the tablets. The binder solution was prepared by mixing the solution of Chitosan (maintained at $4^{o}C$) with the solution of GG or KG or LBG until a homogenous solution is obtained. A temperature of $4^{o}C$ is maintained throughout the experiment. Sustained release tablets were prepared by wet granulation technique using a low-density Natural polymer in combination with chitosan with Guar gum or locust bean gum or Karaya Gum. 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).

Table 1: Composition of burst release highly water soluble tablet containing Metformin HCl.

Formulation Code		Composition of tablet										
	CH (mg)	GG (mg)	LBG (mg)	KG (mg)	Tween (ml)	Olive Oil (ml)	HPMC K4 (mg)	Lactose (mg)	Caco3 (mg)	Metformin Hcl (Mg)	Talc (mg)	MS (mg)
F1	10	10	…	…	2	1.5	100	100	…	650	10	30
F2	10	--	…	..	2	1.5	100	…	100	650	10	30
F3	10	---	10	…	2	1.5	100	100	…	650	10	30
F4	10	---	---	…	2	1.5	100	…	100	650	10	30
F5	10	---	…	10	2	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%.

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 232 nm was measured UV spectrophotometer.

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, India) at 273 nm.

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) and Higuchi's (percentage of drug released vs square root of time).

RESULTS AND DISCUSSION

Drug Excipient Compatibility Studies

The FTIR spectra of pure gums were represented in Fig. 4, showed the IR spectra of LMCH showed the reported IR absorption peaks in the spectra of chitosan. The IR spectra of LMCH exhibited absorption band at 1628, 1380 and 1320cm^{-1}due to amide I, II and III. Absorption band at 3371.3 & 2923.9cm^{-1} are due to hydroxyl stretch and C-H stretch (Fig.4).

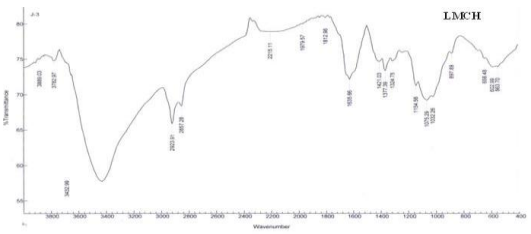

Fig. 4: FTIRSpectra of LMCH.

In the IR spectra of Karaya Gum, a characteristic absorption band at 3371.57 cm^{-1} representing the presence of hydrogen bonded OH group was observed. The 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 (Fig.5-6)

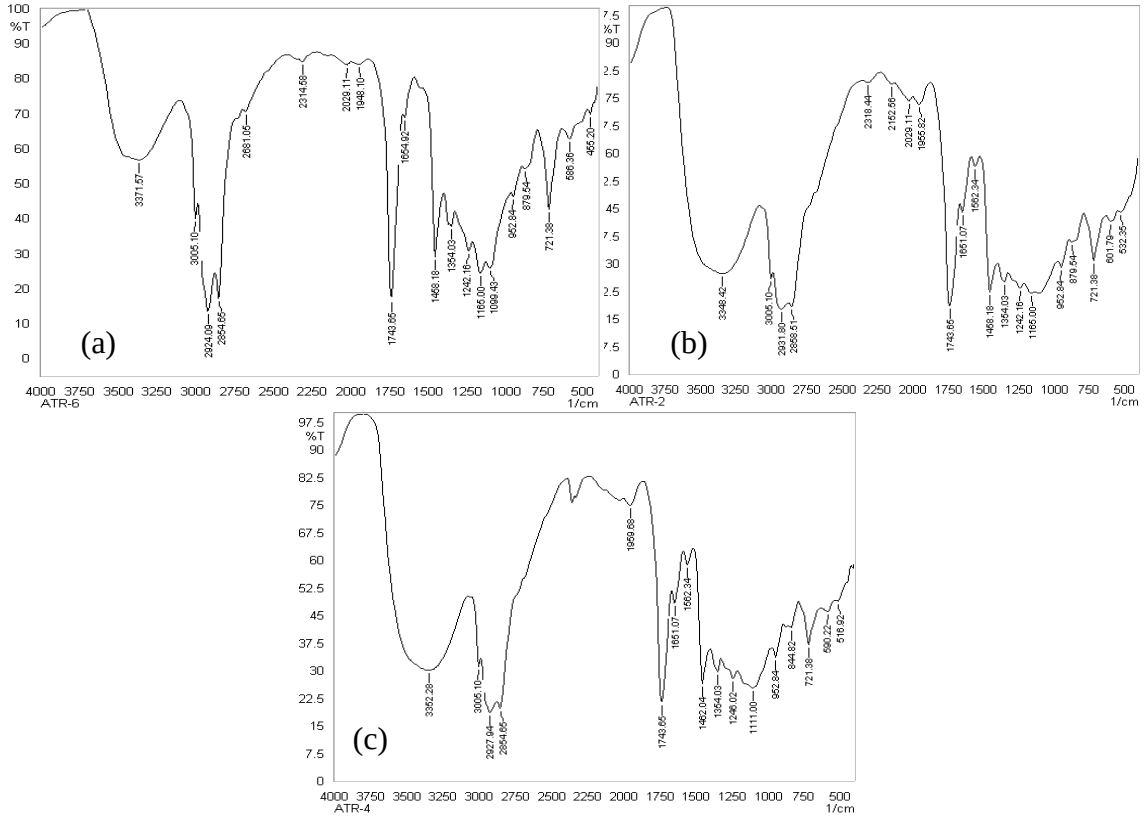

Fig. 5: FTTR spectra of pure gums. (a) Karaya gum; (b) Guar gum; (c) Locust bean gum.

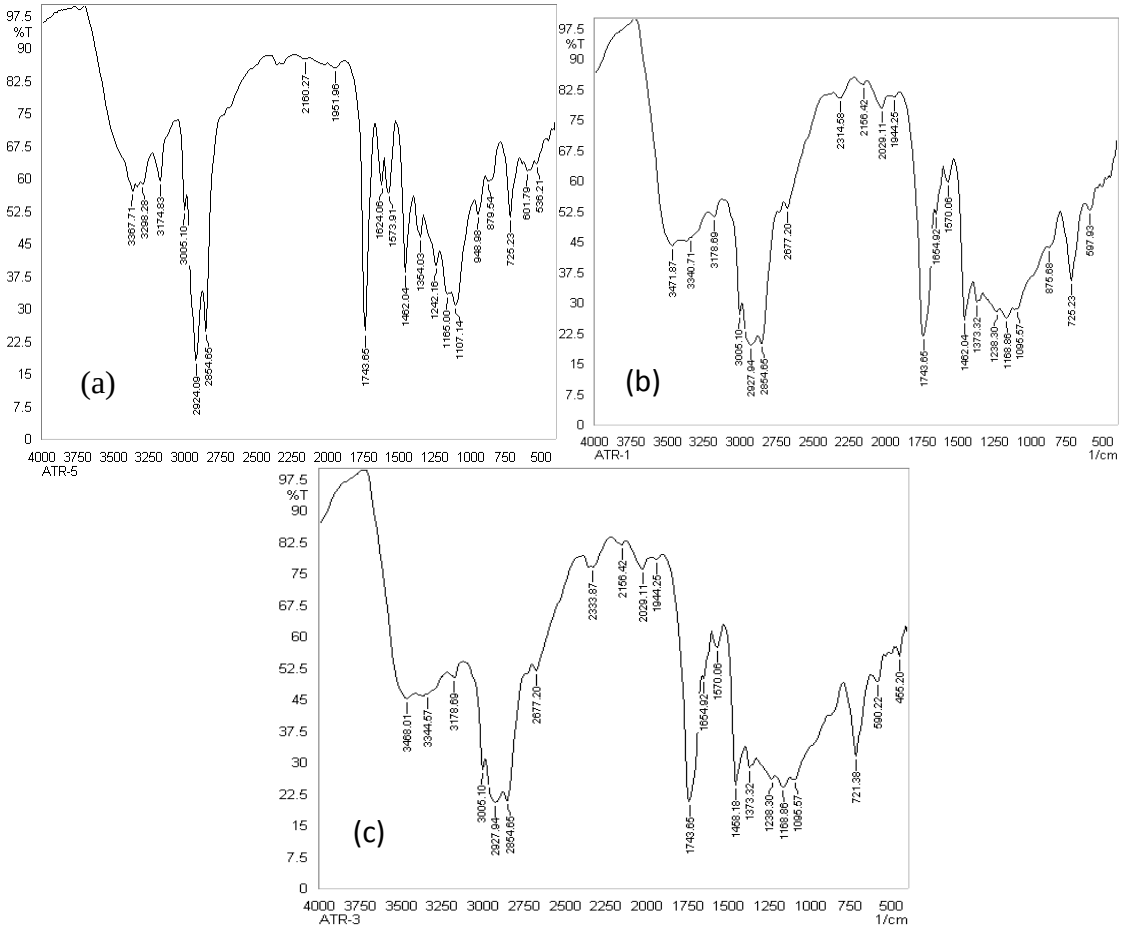

Fig.6: ATR spectra of physical mixture of drug with various gums. (a) Drug with Karaya gum; (b) Drug with Guar gum; (c) Drug with Locust bean gum.

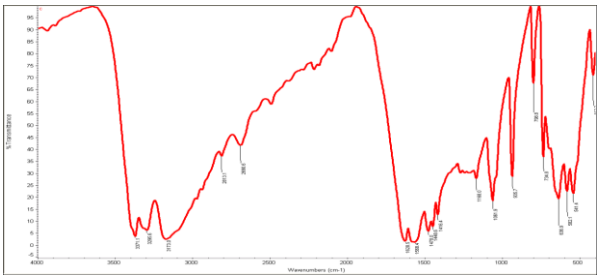

Fig.7: FTIR spectra of pure drug Metformin HCl.

Preparation of Bigels

The homogenized solution of mix in oil was transparent and pale brown in color. The addition of the gum solution to the mix 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 a 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 2. 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. 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 2: 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. The SEM study was carried out for formulated granules of chitosan with three gums (viz karaya gum, guar gum and locust bean gum) to check the surface texture of the same. The Fig. 6.5, 6.6 and 6.7 and showed the micrographs of the granules prepared by CH- guar gum, CH-locust bean gum and CH-karaya gum, 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 (Fig.8-10).

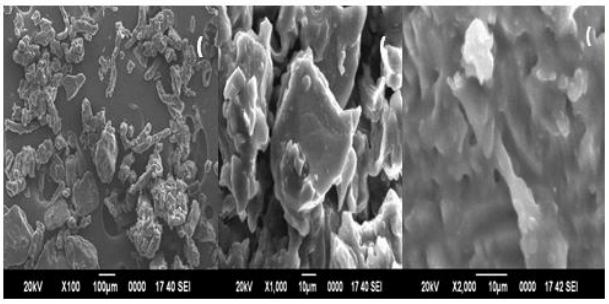

Fig. 8: SEM micrographs of granules prepared by using Chitosan –Guar gum. (a) at 100X, (b) at 1000X, (c) at 2000X.

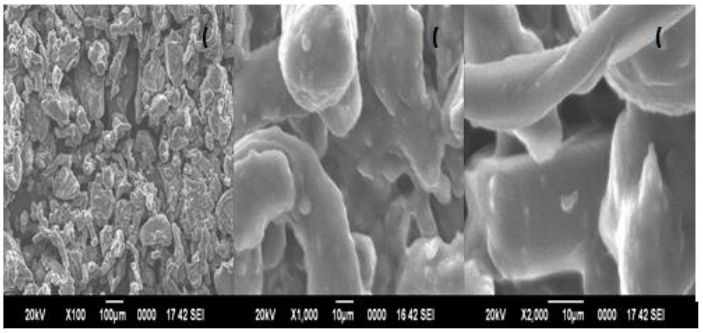

Fig. 9: SEM micrographs of granules prepared by using Chitosan-locust bean gum. (a) at 100X, (b) at 1000X, (c) at 2000X.

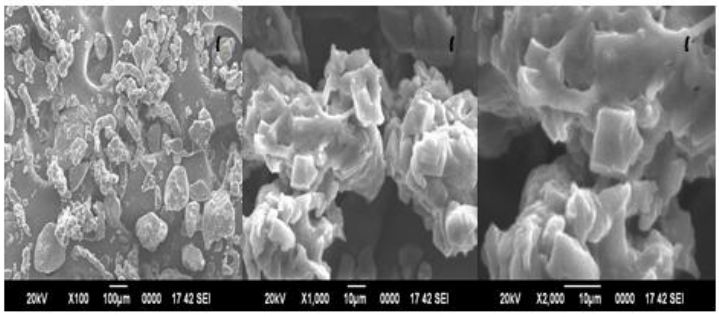

Fig. 10: SEM micrographs of granules prepared by using Chitosan- Karaya gum. (a)at 100X, (b) at 1000X, (c) at 2000X.

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 %.

Fig.11 and Table 3 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 3: Cumulative % Drug release from sustained release tablets of Metformin HCl.

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

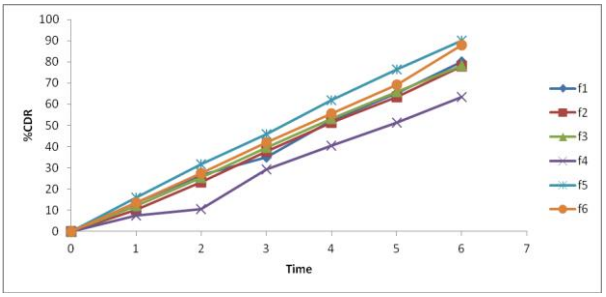

Fig. 11: *Invitro* drug release profile of Metformin hydrochloride from sustained release tablets.

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 HPMC was 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.

Drug release kinetics

The in vitro release pattern of various formulations was analyzed by fitting the dissolution data into various kinetic models. 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 karaya gum was found to be more in comparison to Locust bean gum and Guar gum. The method of bigels preparation by emulsification method has been a novel approach in retarding drug release (Table 4).

Table 4: 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

CONCLUSIONS

Sustained-release (SR) oral delivery systems are designed to achieve therapeutically effective

concentrations of drug in systemic circulation over an extended period of time. The therapeutic benefits of a SR dosage form includes more economical, simple processing, improved efficacy of the drug , reduced adverse events, flexibility in terms of the range in which the drug is to be released and patient compliance. These development of sustained release products for metformin is required to prolong its duration of action and to improve patient compliance. The present study showed the potential use of bigels of the natural gums/polymers (Chitosan in combination with Karaya gum, locust bean gum and Guar gum) 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. This delivery system focuses on reducing the frequency of administration and decreasing the dose-dependent side-effects associated with repeated administration of conventional metformin HCl tablets through diffusion coupled with erosion mechanism .Moreover, drug release from CH- Karaya 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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