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Preparation and evaluation of oral liquid sustained delivery of Metformin HCl

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Abstract

Aims: The aim of the work was to develop an oral liquid sustained delivery form of Metformin HCI (MH) by a simple processing method at low cost. The Primary objective of this system is to ensure safety and to improve efficacy of the drugs as well as patient compliance. This is achieved by better control of plasma drug levels and less frequent dosing. This drug delivery is highly appreciable for geriatric and pediatric patients.

Methods: A Preliminary Research was carried out for the development of oral liquid sustained delivery of Metformin HCl. Various batches of formulations have been developed with varying concentrations of chitosan. The cumulative drug release from optimized formulation was compared with the marketed formulation.

Results: The Oral Liquid Sustained Delivery of Metformin HCl is almost effective like of Conventional Metformin tablets in terms of bioavailability and less toxicity.

Conclusion: The experimental oral liquid loaded Metformin HCl have shown improved efficacy in comparison with conventional Metformin tablets. The invitro studies revealed the success of drug release in a sustained manner.

Key words: Conventional Dosage Forms, Metformin HCl, Oral Liquid, Polymer Dispersion,Sustained delivery, Type-II diabetes.

INTRODUCTION:

Diabetes mellitus is considered as a chronic metabolic disorder which is identified by high blood glucose level caused by insulin deficiency or due to insulin resistance. Apart from regular exercise and balance diet, various hypoglycemic drugs involve to adequately controlling the blood glucose level [1]. Diabetes is a gathering of metabolic maladies caused from imperfect insulin emission or its activity or both coming about hyperglycemia. Insulin is the hormone emitted by pancreas and delivered in blood. The guideline of glucose from blood in body cell is finished by insulin [2]. Pathogenic cycles engaged with advancement of diabetes may run from immune system devastation of β-cells of pancreas to a few irregularities coming about protection from insulin. The anomaly in starch, protein and fat digestion is described by lacking insulin movement.

Metformin HCl [MH] is orally administered biguanides antihyperglycemic drugs used in the preferential treatment of type-2 diabetes [3]. Metformin typically induces adenosine monophosphate-activated protein kinase in the liver, resulting hepatic uptake of glucose and reducing gluconeogenesis through complex effects on the mitochondrial enzymes. The hepatic and peripheral tissue sensitivity of insulin was improved tremendously with the effective use of Metformin HCl. It is hydrophilic in nature and incompletely absorbed form Gastro intestinal membrane. Therefore, it was reported that the absolute bioavailability of 500 mg tablet was only 50-60% [4]. As Metformin HCl shows high aqueous solubility and low intestinal permeability, it is classified under the BCS class III of Bio Pharmaceutics Classification System [5].

It was reported that, conventional Metformin HCl tablets were used for the treatment of type 2 diabetes. The plasma elimination half life of Metformin HCl is relatively short i.e. 1.5 to 4.5 hours [6]. Consequently, to achieve therapeutic efficacy, it is administered 2 to 3 times in a day. The increase in dosing frequency may decrease the patience compliance. Therefore, to rectify such problems, the concept of controlled release drug delivery can be employed for the formulation of Metformin HCl [7]. The controlled release dosage form which is appropriately designed is immensely helpful to gain therapeutic efficacy and safety to the patients. To ensure safety and to improve effectiveness of the drugs, controlled/sustained release dosage form is designed [8]. The concept of different dosage forms like controlled release tablet [9], floating tablet [10], osmotic pump tablet [11], microspheres [12], beads [13] etc. are put forwarded to regulate the release as well as to increase the effectiveness of the drug. Among the various approaches for controlling the drug release, liquid oral sustained release formulation would be the best approach in this regard. Various approaches like sustained release coated microparticles and in situ gelling system are highly implemented in the oral delivery of liquid formulation for controlled/sustained release of the pharmaceutical ingredients. The application of ion exchange like alginates along with chitosan on the oral liquid formulation results on the formation of gel in the stomach as well as in the stomach [14].

The demand of oral liquid sustained medication conveyance frame works in diabetes has demonstrated better conveyance of little atom drugs which may expand the personal satisfaction in diabetic patients. Ordinary dosage type of enemies of diabetics display variety in the bioavailability and shorter half life prompting incessant dosing consequently expanding the symptoms prompting less helpful impact. Considering the states of the diabetes continued medication conveyance-based methodologies are all the more encouraging as far as giving better viability delivery [15].

The tablet and capsules must be gulped down as an entire unit and in the event of dose modification, these can't be broken into equal parts as they are intended for controlled delivery and the gliding capacity additionally relies upon measurements of the tablet. Old and dysphagic patients think that it’s hard to swallow massive tablets and cases. In

such cases, high dosages of the medication can be consolidated into Liquid oral [16, 17].

The biodegradable polymers can give a further authority over medication discharge rates and stays away from the issues identified with the evacuation of the conveyance gadget after medication consumption [18]. Chitosan is a cationic, biocompatible, and biodegradable regular polymer, acquired by antacid deacetylation of chitin. It is a widely contemplated biomaterial in the field of medication/quality conveyance, tissue designing, and food innovation. Because of mucoadhesive property, chitosan nanoparticles can improve oral bioavailability of medications because of their expanded living arrangement time inside the gastrointestinal parcel and expanded contact time with the intestinal epithelium cells, accordingly expanding their take-up.

Different normal and engineered polymers including polysaccharides like carrageenan, gellan gum, gelatin and sodium alginate have been utilized in the advancement experiences a stage progress in nearness of different di and trivalent particles [19-21]. Sodium alginate is a characteristic and hydrophilic polymer reasonable for the entanglement of water-solvent medications [22-24] broadly utilized in pharmaceutical details [25-27]. HPMC is utilized as a consistency modifier. Sorbitol is utilized as a sugar in liquid orals and studies have indicated that gels containing 10-17 % Sorbitol continued the arrival of medication in rodent stomach and a bioavailability of roughly 90% was accomplished from orally directed syrups [28-30].

The constraints related with the traditional structures require the advancement of novel details that can convey the medication straightforwardly at a diminished dosing recurrence. Among the transporters for supported delivery, polymeric particles, liposomes and strong lipid nanoparticles (SLNs) have been used to embodied for controlling release [31]. Considering the way that Oral Liquid Sustained Delivery of Metformin has great biocompatibility, great security and the property to expand tranquilize discharge [32]. Polymeric Suspensions may be used as a transporter for the exemplification and continued conveyance of Metformin HCl. Along these lines, in the current examination, the primary goal was to detail Metformin HCl in the type of oral liquid Sustained Delivery and to assess its in vitro exhibition and in vivo Studies.

The research work focused on the turn of events and assessment of a coasting, oral liquid measurement type of Metformin HCl for continued delivery, alongside giving proof seeing tweaked sedate delivery according to legitimate details. No oral liquid supported delivery plans of Metformin HCl are accessible in market on today and consequently an endeavor is being to build up the equivalent.

MATERIALS AND METHODS

Materials:

Metformin HCl, Chitosan, Calcium carbonate, Sodium Benzoate, Sodium TriPolyphosphate, Sodium Citrate were obtained from Yarrow Chem Products, Mumbai.

Methods:

Pre-formulation studies:

Drug-excipient compatibility studies by FT-IR

To investigate any possible interaction between the drug and polymers used, the IR spectrum of the pure drug (MH) and the binary mixture of drug and polymers was taken using FTIR (UV visible spectrophotometer, Alpha Bruker) [33-35].

Design of experiment and statistical optimization

The regular strategies for experimentation by transforming each factor in turn being tedious, the Design of Experiment (DOE) was finished utilizing the JMP Statistical Software (Trial variant 13). The polymers and different amounts were chosen dependent on announced writing on comparative investigations and starting screening tests done to distinguish the ideal conditions and amounts required. Assessment of primer groups was done dependent on reactions, for example, in vitro release considers, drug delivery and pourability (relative consistency), to choose the working focus scope of polymers (factors).

Formulation of Oral Liquid Metformin HCl by Polymer Dispersion Method

Metformin HCl was prepared by Polymer dispersion method. An accurate amount of Metformin hydrochloride dissolved in 5 mL of water using sonicator for 5 mins for complete solubility. Now, specified amount of chitosan (Table 1) were dispersed in aqueous solution of glacial acetic acid and stirred by magnetic stirrer for 1 h. The aqueous solution of drug is poured slowly into the aqueous solution of glacial acetic acid containing chitosan with continuous stirring and 20 mg of sodium benzoate is dissolved in 2.5 mL of water which is used as preservative and transferred to the formulation with continuous stirring for 1h at 600 rpm and 10 mg of Sodium Trioly Phosphate dissolved in 2.5 mL of water and transfer to the formulation.

Evaluation:

pH of the Formulation:

The pH of the formulation was determined using a calibrated pH meter and readings taken in triplicate [36, 37].

Viscosity:

The thickness of the solution was resolved utilizing Brookfield viscometer (DV-II+ Pro LV model). The choose plans (250 mL) were filled the example connector of the viscometer and the consistency estimated at room temperature utilizing SC4-18 axle for the solutions. The precise speed was step by step expanded from 10 to 50 rpm with a 6 sec pause period, the chain of command turned around and the normal taken. The consistency estimations were made in triplicate [38].

Determination of Drug Content:

Around 50 mg of Metformin Hydrochloride identical to Oral Liquid Suspension was dissolved in 50 mL of water and sonicated for 45 minutes. At that point 10 mL of the above arrangement was diluted to 100 mL with water. 1 mL from the above arrangement was taken and diluted to 10 mL with

water and estimated at 232 nm under UV spectrophotometer and the level of medication content was determined.

In vitro drug release and kinetics:
The drug release study was completed utilizing USP Type II dissolution device (Paddle type, Electrolab). 1 mL of the definition equal to 500 mg/mL was kept in Dialysis Membrane and dissolution done. At predetermined time stretches, 1 mL of test arrangement was withdrawn, separated through a 0.45µm membrane, reasonably diluted and analysed by UV spectrophotometrically at 232 nm. A similar measure of new dissolution medium was supplanted following withdrawal of the test [39-41]. The system of drug was concentrated by fitting the dissolution information in the zero-request, first-request, Higuchi model and Korsmeyer-Peppas condition following model-subordinate energy. Based on the slope and r^2 Optimization values obtained, the mechanism of drug release was determined [42-45].

Optimization:
The qualities got in the wake of assessing the reactions tentatively were taken care of into the JMP programming and the information examined. The mathematical enhancement methods and the least square fit model were utilized. The attractive quality methodology (utilizing Prediction profiler) was used to produce the ideal settings for the plan. Advancement was accomplished for the reactions by keeping drug release at 1h at most extreme while that at 8 h and 12 h were kept in the range [46]. The advancement target and limitations were set dependent on the official IP details.

Statistical Analysis:
Statistical analysis was carried out using the ANOVA and p-values less than 0.05 were considered statistically significant.

Stability Studies:
Accelerated stability studies were directed according to ICH Q1C rules on the streamlined detailing to survey the soundness with regard to physical appearance, drug substance anddrug release attributes in the wake of putting away in a stability chamber (Thermolab) at 40 °C/75% (RH) for 6 months. The product was filled in a HDPE bottle with sealed CRC caps [47, 48].

RESULTS AND DISCUSSION:

Preformulation study:

Drug-excipient compatibility studies by FT-IR:
No critical movements or decrease in the force of the FTIR groups of MH were seen as illustrated in the Figure 1.These groups were additionally watched for the physical blend of polymers alongside MH, in this manner affirming that there was no interaction between MH, polymers and excipients utilized and that they were viable with the drug.

Metformin HCl liquid Oral Sustained Formulation:
In this research work, formulations were prepared in which Chitosan were used as drug carrier. The chitosan is used as coating agent to the pure drug in order to reduce impact on their body and increase their bioavailability.

***In vitro* Drug Release Studies:**
The in vitro drug release studies for the Metformin HCl formulation and optimized formulae were done and the results compared with the marketed conventional dosage forms (Table 4). The drug release data fitted into the various models showed very close r^2 values (above 0.8).
The r^2 values of the Higuchi model of all the formulations showed higher values indicating that the drug release was directly proportional to square root of time. But n values ranging from 0.2033 to 0.5239 indicated Fickian diffusion mechanism. It may be coincident. However, n values of Korsmeyer-Peppas strongly indicated Fickian diffusion.

Stability studies:
Stability studies carried out on the optimized formulation as per ICH guidelines (Q1C) revealed no significant changes in the physicochemical properties, viscosity or drug release of the formulation even on the aging of the liquid orals under the different storage conditions.

Table 1: Composition of Oral Liquid Metformin HCl by Polymer Dispersion Method

Formulation Code	Drug (mg)	Drug: Chitosan	Sodium Benzoate (mg)	Sodium TPP (mg)	Cold water (mL)	Glacial acetic Acid (mL)
R1	400	100:100	20	10	10	70
R2	300	200:400	20	10	10	70
R3	400	100:200	20	10	10	70
R4	300	200:200	20	10	10	70

Table 2: Optimized formula (R5) of Metformin HCl suspension by DOE

S.No	Ingredients	Quantity(mg)
1	Metformin Hydrochloride	382.5
2	Chitosan: Drug	221.88:178.12
3	Sodium tri-polyphosphate	20
4	Sodium benzoate	10
5	Cold water	5 mL
6	Glacial acetic acid (1%)	1

Table 3: Response variables of the various batches of formulations

Formulation Code	pH	Viscosity (Cps)	Drug Content (%)	Entrapment efficiency	*In vitro* Release (%) (12 h)
R1	7.1	420	91.25	87.15	92.03
R2	6.9	390	89.20	85	86.61
R3	6.8	540	84.20	82.5	83.91
R4	7.1	380	80.50	83	81.20
R5	7.2	400	91.25	87.15	92.03

*R5 is optimized formulation

Table 4: Comparison of drug release profile of optimized formula(R5) with marketed product

Time(h)	%CDR (Optimized Formula-R5)	%CDR (Marketed Product)	IP specifications
0	0	0	Not less than 25% and not more than 50% in 1 hour
1	39.248	42.366	
2	50.075	51.251	
3	67.669	69.336	Not less than 45% and not more than 75% in 3 hours
4	70.376	72.001	
5	73.083	74.456	
6	75.789	77.123	
7	78.496	79.821	
8	83.910	84.125	
9	86.617	85.125	
10	92.030	95.123	Not less than 80%.

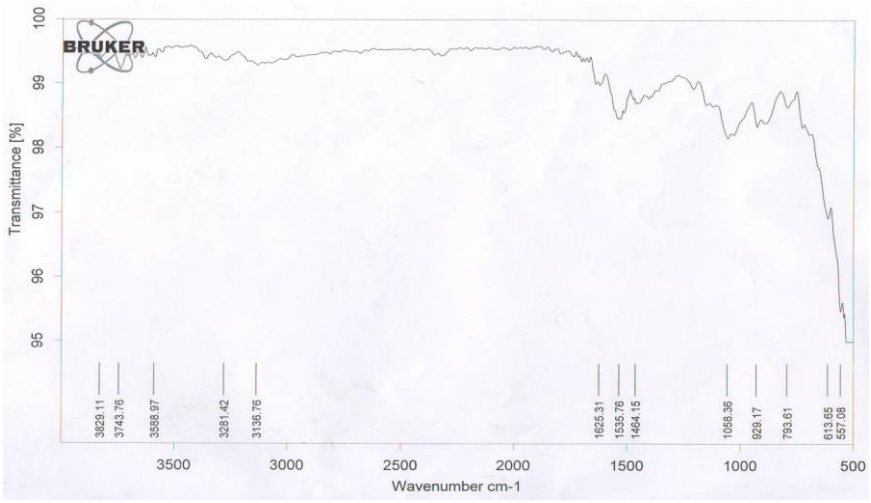

Figure 1: FT-IR peaks illustrating the compatibility of Metformin with Excipients

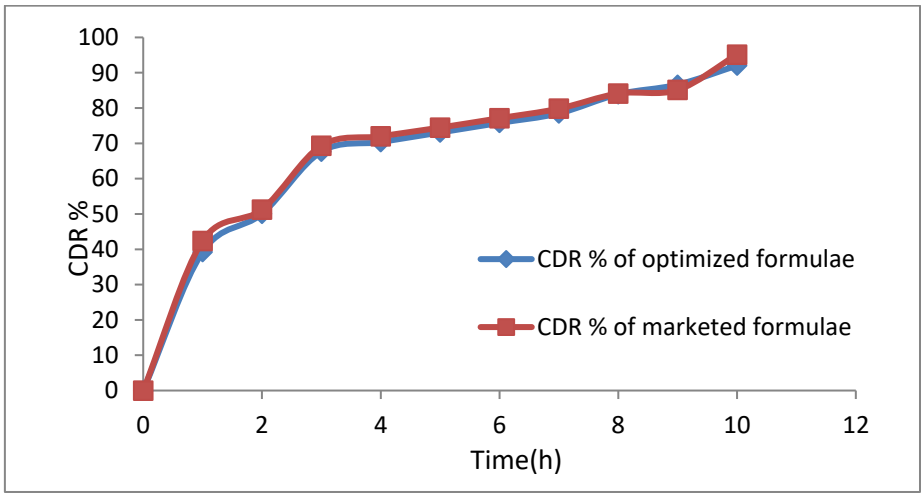

Figure 2: Comparison of CDR % of Optimized formula (R5) with Marketed Dosage Form

CONCLUSION AND FUTURE SCOPE OF WORK:

It tends to be reasoned that a promising, stable supported delivery, oral liquid frameworks of Metformin Hydrochloride that met the official determinations of sustained delivery could be effectively evolved utilizing Statistical design and optimization techniques. Therapeutic concentrations of the drug could be accomplished in plasma in a sustained manner and the drug release was supported for 12h when contrasted with the marketed conventional dosage forms (tablets).

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