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FORMULATION AND EVALUATION OF METFORMIN AS A FAST DISSOLVING TABLET BY MELT GRANULATION TECHNIQUE

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ABSTRACT

The study "Formulation and evaluation of mouth dissolving tablets of Metformin HCl" revealed that the FTIR study it is confirmed that no interaction took place between the drug and other excipients used in the formulation procedures. The characteristic peaks of the pure drug were compared with that obtained with different blends which nearly same. The thin layer chromatographs of pure drug and that of different formulation blends confirmed approximately equivalent Rf values. Conclusively metformin HCl was found to be compatible with both polymers and other ingredients incorporated in the formulations. The Various physicochemical parameters determined with the tablets were bulk density (0.4-0.73g/cc), tapped density (0.64-0.85g/cc), carr's index (14-34%), angle of repose (30-44) and Hausner ratio (1.22-1.54). Other evaluation parameters included in-vitro drug release in buffer systems (98%-100%) and in simulated physiological media (98%-100%). The *in-vitro* release of the drug with best formulation (B3) in simulated medium was found to be 99.67% which showed fast release over a period of 30 mins. The stability study was performed with the optimizied formulation (B3) under prescribed conditions which showed that these formulations were stable and thus complied with dose conformity criteria.

KEYWORDS

Metformin, Chromatograph, Stability and Physiochemical.

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INTRODUCTION

Oral drug delivery is the safest, most convenient, and most economical method of drug delivery with the highest patient compliance. However, the most obvious drawback of commonly used oral dosage forms such as tablets and capsules is that drug administration is difficult to swallow, leading to patient non-compliance, especially in pediatric and

geriatric patients[1]. One study showed that 28% of her 1567 patients had difficulty swallowing the pill because of its size (the pill)[2].

Recently, further research has been conducted to develop sensorily elegant and patient-friendly drug delivery systems for pediatric and geriatric patients. Therefore, a new delivery system known as fast dissolving/disintegrating (FDDS)/orally dissolving tablets has attracted attention. This type of oral dosage form dissolves quickly in saliva and can be swallowed without water. Elimination of bitterness is an important criterion in the formulation of orally disintegrating tablets.

Orally Disintegrating Tablets come in two types: buccal type and sublingual type. These two classes of tablets are designed to be held in the mouth and release their drug content for direct absorption through the oral mucosa. These tablets are usually small and somewhat flat and intended to be held between the cheek and teeth, or in the cheek pouch (oral tablets) or under the tongue (sublingual tablets). All FDA-approved fast-dissolving tablets are classified as orodispersible tablets. The European Pharmacopoeia defines the term "orally dispersible" as a tablet that can be placed in the mouth and dissolves quickly before swallowing[3].

The Center for Drug Evaluation and Research (CDER) of the US FDA has we defined an disintegrating tablet (ODT) as "a solid dosage form containing a drug that dissolves rapidly, usually within seconds, when placed on the tongue[4]. When is placed in the oral cavity, saliva quickly enters the pores, causing swelling and rapid disintegration of the tablet.

So the basic approach to developing MDT is[2]:

Maximize the porous structure of the tablet matrix.

With suitable explosives.

Use of highly water-soluble excipients in formulations.

Properties of Orodispersible Tablets in the Mouth[1-2]

Does not require water to swallow and dissolves in the mouth at body temperature within seconds.

Allows high drug loads.

Compatibility with taste masking and other additives.

Pleasant mouthfeel.

Little or no residue is left in the mouth after oral administration.

Strong enough to withstand rigorous manufacturing processes and post-manufacturing handling.

Less sensitive to environmental conditions such as humidity and temperature.

Adapt and access existing processing and packaging equipment.

Enables cost-effective manufacture of tablets using conventional processing and packaging.

Salient Features of Mouth Melt Tablet[s5]

MMT provides an ease of administration to the patients who cannot swallow e.g. elderly, stroke victims, bedridden, those affected by renal failure, pediatric, geriatric and psychiatric patients.

These dosage forms provide rapid melting, dispersion, dissolution and absorption of the drug leading to quicker onset of action.

MMT provides pregastric absorption resulting in improved bioavailability of the drug thus reducing the effective dosagic concentrations and dosing frequency.

No chance of temperature-based degradation as drying is not required.

These dosage forms provide new business opportunity like product differentiation, product promotion, patent extensions and life cycle management.

These drug delivery systems are beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing where an ultra rapid onset of action is required.

MMT are stable on storage for longer duration of time as stored at low temperature.

MMT can be taken while traveling without need of water.

Advantages over limitations of mouth dissloving tablets[6]

The MDT's usually have insufficient mechanical strength and hence, careful handling is required while mouth melt tablets, showed better hardness on storage.

The MMT's may leave unpleasant taste and/or grittiness in mouth if not formulated properly while

mouth melt tablets have a minimum amount of water insoluble matter.

Excipients used in orodispersible tablets[7-10]

Excipients play a very important role in the formulation of orodispersible tablets. These inert, food-grade ingredients, when incorporated into formulations, impart desirable sensory attributes and product efficacy. Excipients are common and can be used for a wide range of active ingredients except those that require sequestering agents.

Filler

Acts as a diluent, filler, cost saving. Bulking agents recommended for this delivery system should be based on more sugars such as mannitol, polydextrose, lactitol, DCL (directly compressible lactose) to achieve higher water solubility and better sensory perception. I have. Fillers are added in the range of 10% to about 50% by weight of the final composition.

Anti-adhesive: Essential adjuvant, provides anti-stick properties and reduces hygroscopicity. It also helps make such tablets more palatable after dissolving in the mouth. The addition of these ingredients helps overcome the bitterness and undesirable taste of some of the active ingredients. Choose from a wide range of sweeteners including dextrose, fructose and more.

Meltable Polymers: PEG and PEG Blends

Oral Oral Orodispersible Tablet Manufacturing Technology

Melt granulation technology has been developed for the manufacture of selected oral dissolution drug delivery systems for oral melt formulations as follows.

Melt granulation[11] Powders use dissolved liquids as binders (fusible binders), which remain components of the formulation and can be efficiently agglomerated. This approach to manufacturing orodispersible tablets with sufficient mechanical integrity involves the use of hydrophilic polymers (superpolysylate, PEG-6 stearate). Superpolysylate is a waxy substance with a melting point of 33-37°C and an HLB value of 9.

As such, it acts as a binder and not only increases the physical strength of the tablet, but also aids in tablet disintegration by providing a melt-in-the-mouth dissolution and rapid dissolution without leaving a residue.

The advantage of this technology over conventional granulation is that neither water nor organic solvents are required. Because there is no drying step, the process takes less time and uses less energy than wet granulation. It is a useful technique to improve the dissolution rate of poorly water-soluble drugs such as griseofulvin.

Agglomerates can be divided into he two types of granules and pellets.

Granules are irregularly shaped agglomerates with a rather broad size distribution, usually between 0.1 and 2mm.

Pellets are spherical aggregates with a narrow size distribution ranging from 0.5 to 2mm.

The most common method of characterizing molten agglomerates is to determine the average agglomerate size and size distribution by sieving.

An *in vitro* dissolution study was performed to investigate the drug release properties of the melt agglomerates. However, a quantitative relationship between the *in vivo* and *in vitro* performance of molten agglomerates is still generally lacking. Another important property of molten agglomerates is their performance stability during storage. It was found that molten agglomerates can maintain their dissolution profile after 1 year of storage at 25°C and 60% relative humidity, say 100%. B: The release of sulfamethazine from tablets manufactured from melted granules remained unchanged after 2 years of storage at 25°C in a closed container. Due to the meltability of the agglomerates, stability tests are preferably performed at appropriately selected storage temperatures without significant changes in the physico-chemical state of the agglomerates.

Mechanism of melt aggregation[12].

The growth process of molten agglomerates depends on the interplay of expansion and fragmentation processes. The likelihood of agglomerates increasing in size or breaking up is a result of the balance between the externally applied mechanical force and the strength of the

agglomerates. Aggregates grow in size if they have sufficient strength to withstand exposure to externally applied forces or vice versa. Aggregate strength is affected by the relative magnitudes of capillary, frictional, and viscous forces. Capillary forces help solidify agglomerates by pulling solid particles together, while viscous and frictional forces resist both solidification and expansion of solid particle aggregates. The aggregation process consists of a combination of three stages: wetting and nucleation, solidification and growth and attrition and decomposition[12].

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Wetting and Nucleation

Nucleation is the initial stage of aggregation, in which nuclei or small aggregates with loose porous structures are formed after primary particles are wetted by binding droplets. In the pendulum state, the primary particles are bound by liquid bridges. The liquid saturation of the agglomerates can be increased by continuously adding liquid or coagulating the agglomerates. Schaefer and Mathies propose his two nucleation mechanisms, immersion and dispersion, based on melt-agglomeration processes. The dominance of each mechanism in the melt-agglomeration nucleation process is a function of the size ratio between the primary particles and the molten binder droplets.

Nucleation by immersion occurs when the molten binder droplet is larger than the solid particulate droplet[13]. Dipping is caused by the deposition of solid particulates on the surface of molten binder droplets. The propensity for nucleation from the immersion process is driven by large binder droplet size, high binder viscosity and low shear force. This reduces the chance of the molten binder droplets breaking up and keeps them relatively large in size, several times the size of the fines solid particles.

In nucleation by diffusion, a molten binding liquid diffuses to the surface of a solid particulate. The nucleus is formed by collisions between wet particles. The cores formed have a loose structure with trapped air, in contrast to those produced by the dipping process. In general, small binder droplet size, low binder viscosity and high shear force are favorable conditions for nucleation by the dispersion process. The nucleation stage is characterized by the disappearance of fines as a result of coalescence between wet or nucleated primary particles. The resulting core solidifies under the influence of externally applied mechanical forces, gaining sufficient strength to resist further collapse due to impact forces, and may grow into larger agglomerates.

Integration and growth[14]

The probability of successful fusion between colliding cores depends on the liquid saturation of the cores. During the agglomeration process, the agglomerates are coagulated by the stirring force. The reduction in aggregate pore size and number facilitates the transfer of binding liquid from the aggregate core to the surface, improving surface plasticity and aggregate growth propensity through coalescence. The rate and extent of aggregate solidification is governed by interparticle frictional, capillary, and viscous forces. Frictional and viscous forces between particles resist the consolidation process of agglomerates.

Technology and its relevance to present study[15]

Metformin HCl belongs to a class of biguanides (oral hypoglycemic drugs) that have long been used to treat non-insulin dependent diabetes. Metformin is highly soluble in water and poorly permeable to

cell membranes. Therefore, it can be classified as a BCS class III drug. Absorption of metformin following oral solution administration is slow and incomplete, with the solution formulation being bioequivalent to an immediate release tablet and completely dissolving within an hour. Therefore, it is clear that if the metformin immediate-release product formulation dissolves rapidly, the dissolution does not affect the bioavailability of metformin.

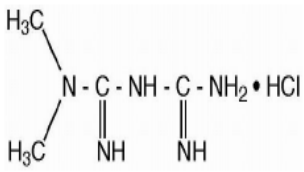
The usual dose of metformin is 250-500mg three times a day, up to a maximum of 3g/day. The absolute bioavailability of 500mg immediate-release metformin HCl tablets administered under fasting conditions is 50-60%. Peak plasma concentrations occur approximately 2.5 hours after oral administration. Absorption of metformin from the gastrointestinal tract is dose-dependent, with food slightly decreasing both the rate and extent of its absorption. Occurs in the gastrointestinal tract. Metformin is associated with severe lactic acidosis, especially in patients with renal impairment.

Current collaborators focused on the primary objective of increasing drug bioavailability in the context of dissolving the tablet in the mouth, reducing its size compared to conventional tablets, and improving absorption. We devised the design of metformin mouth-dissolving tablets. Improves in the upper abdomen of the GIT. This formulation tends to improve ease of administration coupled with improved patient compliance, especially in the elderly and bedridden.

Market research reveals that most of the available dosage forms are conventional extended release tablets. Some prescribers have published articles on 250mg orally disintegrating tablets.

Profile[16,17]

Name: Metformin Hydrochloride

Structure	

Physicochemical Profile

Molecular Formula: C4H11N5.HCl

IUPAC Name: N, N-Dimethylimidodicarbonimide Diamide Hydrochloride

Molecular Weight: 165.62 Daltons

Category: Antihyperglycemic Drugs

Description: White to off-white crystalline, hygroscopic

Solubility Metformin HCl is sparingly soluble in water, sparingly soluble in ethanol, and practically insoluble in acetone, ether and chloroform.

Pharmacokinetic Profile

Plasma Half-Life: 6.2 hours.

Duration of action

Oral bioavailability: 8-12 hours

50-60%

Mechanism of action[12]

Systemic energy balance and carbohydrate and lipid metabolism. Activation of AMPK is required for the inhibitory effect of metformin on glucose production by hepatocytes. Increased peripheral glucose utilization may be due to improved insulin binding to insulin receptors. Metformin administration also increases AMPK activity in skeletal muscle. AMPK is known to induce her GLUT4 release at the plasma membrane, resulting in insulin-independent glucose uptake.

EXCIPIENTS PROFILE[18-20]

Proprietory Name: Polyethylene Glycol 1000[49]

Nonproprietary Names: BP : Macrogols; JP: Macrogols 1000; PhEur: Macrogols; USP-NF: Polyethylene Glycol

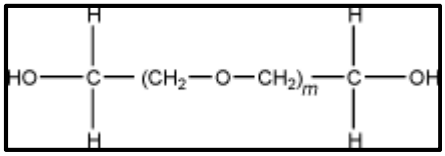
Synonyms: Carbowax; Carbowax Sentry; Lipoxol; Lutrol E; macrogola; PEG; Pluriol E; polyethylene glycol.

Chemical Name: α-Hydro-ώ-hydroxypoly (oxy-1, 2-ethanediyl)

Empirical Formula

HOCH2(CH2OCH2) mCH2OH where m represents the average number of oxyethylene groups.

Structural Formula



Functional Category

Ointment bases; plasticizers; solvents; bases for suppositories; lubricants for tablets and capsules.

Applications in Pharmaceutical Formulations or Technologies:

PEG is widely used as an excipient in a variety of pharmaceutical formulations, including parenteral, topical, ophthalmic, oral, and rectal formulations. Polyethylene glycol is used in biodegradable polymer matrices used in controlled release systems.

PEG is an inherently stable, hydrophilic substance that is essentially non-irritating to the skin.

Polyethylene glycol has the following disadvantages[20-26]

More chemically reactive than fat. Great care must be taken in processing to avoid non-elegant shrinkage holes in the uvula. The release rate of water-soluble drugs decreases as the molecular weight of polyethylene glycol increases, and polyethylene glycol tends to irritate mucous membranes more than fat. In solid dosage forms, high molecular weight polyethylene glycols can improve the effectiveness of tablet binders and impart plasticity to granules. It has limited binding activity when used alone and can prolong decay when present at concentrations greater than 5% w/w. For use in thermoplastic granules, heat a mixture of powdered ingredients with 10-20% (w/w) PEG 6000 to 70-80°C. The mass becomes pasty and forms granules. This technology is used to manufacture lozenge dosage forms that require long disintegration.

Polyethylene glycol has been used in the preparation of urethane hydrogels used as controlled release agents. PEG has also been used in insulin-loaded microparticles for oral delivery of insulin. Used in inhaled formulations to facilitate aerosolization. PEG nanoparticles have been used to improve the oral bioavailability of cyclosporine. It has been used as a drug carrier for self-assembled polymeric nanoparticles and copolymer networks of polyethylene glycol grafted with polymethacrylic acid have been used as bioadhesives for controlled drug release.

Typical properties[15,16]

Density - 1.15 to 1.21g/cm3 at 25°C for solid PEG. As (1.08g/cm3)

Hydroxyl number - 106-118

Viscosity - 22-30mPa (dynamic) 20.4-27.7mm2/s

Melting point - Same as PEG 1000, melting point 37-40°C

Moisture content – Liquid PEG in particular is very hygroscopic and can become less hygroscopic as the molecular weight increases.

Solubility - All PEG grades are soluble in water, solid PEG is soluble in acetone dichloromethane. Soluble (95%) in ethanol and methanol. It is slightly soluble in aliphatic hydrocarbons and ethers, but insoluble in fats, fatty oils and mineral oils.

Stability and Storage Conditions:

Polyethylene Glycol is chemically stable in air and in solution, but types with molecular weights less than 2000 are hygroscopic. Polyethylene glycol does not support microbial growth and does not turn rancid.

Polyethylene glycol and aqueous solutions of polyethylene glycol can be sterilized by autoclaving, filtration, or gamma irradiation. Sterilization of solid grades by dry heat at 150ºC for 1 hour can cause oxidation, darkening, and the formation of acidic degradation products. Ideally, sterilization should be done in an inert atmosphere. Oxidation of polyethylene glycol can also be inhibited by including appropriate antioxidants. The Heated Tank is used to hold polyethylene glycol, which is normally a solid, in a molten state care should be taken to avoid iron contamination which causes discoloration. The temperature should be kept at the lowest temperature required for fluidity. Oxidation can occur when polyethylene glycol is exposed to temperatures above 50°C for extended periods of time. Store PEG in a closed container in

a cool, dry place. Storage under nitrogen reduces the possibility of oxidation.

MATERIAL AND METHODS

Materials

Various materials used to manufacture metformin hydrochloride orally dispersible tablets. H. APIs, additives, reagents, etc. were sourced from various reputable companies as summarized below.

EXPERIMENTAL WORK

Preparation of standard calibration curve in phosphate buffer pH 6.8 Preparation of stock solution

Metformin HCl stock solution (10µg/ml)

50mg of drug was accurately weighed and transferred to a 50mL volumetric flask. The drug was then dissolved in 50ml of phosphate buffer (pH 6.8) and further diluted to give a stock solution of drug of 10µg/ml. Estimation of λ max: A sample of 10µg/mL stock solution was scanned from 200 to 400nm to access the λ max of metformin HCl, reproduced and verified by overlaying UV spectra of different concentrations. Did, Me. H. 2, 4, 6, 8, 10µg/ml. Preparation of aliquots: Appropriate serial dilutions ranging from 1 to 10µg/ml were made from the stock solution and the absorbance was recorded at the given wavelength. A standard calibration curve was obtained by plotting absorbance against concentration (µg/mL).

Preparation of Simulated Saliva

Simulated Saliva was prepared using the following ingredients and mixed with gentle agitation in approximately 800mL of deionized water in the order listed below.

After all the ingredients dissolved, the solution was made up to 1 litre and mixed thoroughly at room temperature.

A 25ml sample was analysed for pH and found to be in the range of 6.5±0.2.

The solution was filtered once through 0.45µm and then passed through 0.2µm micropore filters. Due to the viscous nature of the solution, filters became clogged so it was necessary to change filters oftenly.

Drug polymer compatibility studies

By thin-layer chromatographic method (As per E.P.)

The drug polymer compatibility was also confirmed by TLC evaluation using glass plates precoated with silica gel ($60F_{254}$) and glacial acetic acid-butanol-water in the ratio of 1:4:5 (v/v) respectively as mobile phase. The evaluation of separated spot was performed by running in a saturated TLC chamber and visualized in iodine chamber.

EVALUTION PARAMETERS

Pre compression parameters

Bulk density (D_b)[62]

It is the ratio of total mass to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted and expressed in gm/ml.

$$D_b = \frac{M}{V_O}$$

Where, M= The mass of powder; V_0= The Bulk volume of the powder

Tapped Density (D_t)

It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume expressed in gm/ml.

$$Dt = \frac{M}{V_t}$$

Where, M= The mass of powder; V_t= The tapped volume of the powder

Carr's Index (I)

It indicated the ease with which a material could be induced to flow and expressed in percentage.

$$I = \frac{D_t - D_b}{D_t} X\ 100$$

Where, D_t= The tapped density of the powder; D_b= The bulk density of the powder.

Angle of Repose

The frictional forces in a loose powder was measured by the angle of repose "θ" which is the maximum angle possible between the surface of a pile of powder and the horizontal plane. tan $= \frac{h}{r}$

$$= tan^{-1}(\frac{h}{r})$$

Where, θ = The angle of repose; h = The height in centimeters; r = The radius.

The powder mixture was allowed to flow through the funnel fixed to a stand at the definite height. The angle of repose was calculated by measuring the height and radius of the heap of powder formed.

Hausner Ratio

Hausner ratio is defined as the ratio of Tapped density upon Poured density.

FORMULATION DESIGN

Preparation of tablet

For above batches of formulations, first PEG1000 and cremophor were melted in a beaker (at 60ºC) with gradual addition of Metformin, Talc and D-Manitol were mixed vigorously to form granules and then passed through sieve no. 20.

Aspartame, Monoammonium glycrizinate and Mint flavor were mixed in the prepared granules and passed through sieve no. 20, talc was mixed as lubricant. The resultant mass was compressed to form tablets (quantity as per master formulation).

EVALUATION

The prepared Tablets were evaluated for the following parameters:

General appearance

The 'elegance', is essential for consumer acceptance.

Size and shape

At a constant compressive load, tablet thickness varies with changes in die fill, particle size distribution and packing of the particle mix being compressed and with tablet weight. While with a constant die fill, thickness varies with variations in compressive load. The crown thickness of individual tablets may be measured with a micrometer.

Tablet thickness was controlled within a ±5% variation of a standard value.

Uniformity of dispersion

Two tablets were placed in 100ml of water and stirred gently until completely dispersed. A smooth dispersion was obtained which was passed through a sieve screen with a nominal mesh aperture of 710 mm (sieve number 22).

Drug content uniformity

5 tablets were dissolved in 100ml buffer separately, diluted to be in range of 1-10µg/ml and evaluated for drug content uniformity.

Weight variation

10 tablets were weighed separately, compared with the labeled claim and accepted if not more than 2 tablets are outside the 5% limit and if no tablet differs by more than 2 times the percentage limit.

***In-vitro* dissolution test**

Metformin HCl

USP Apparatus: 2 (paddle type)

Speed (rpm): 50

Medium: Phosphate buffer, pH 6.8/ Simulated Salivary Fluid

Volume (mL): 500

Recommended Sampling Times (minutes): 5, 10, 15, 20, 30 and 60 min.

Temperature: 37ºC±0.5ºC.

***Ex-vivo* Study**

Ex-vivo studies were performed for the optimized batch (with best taste masking and dissolution profile). Study was performed on Frandz diffusion cell and excised cock pouch was utilized as the permeable membrane. Simulated salivary fluid was used for the experiment and magnetic stirrer with hot plate was used to maintain temperature and circulation of fluid within lower or receiver compartment. Samples were taken at different time intervals and evaluated.

Accelerated stability study

The stability study of tablet was carried out for a period of 90 days at 30±2°C temperature and relative humidity of 65±5% using stability chamber. Sample was collected after 45 & 90 days and evaluated for routine parameters.

RESULTS AND DISCUSSION

Experimental studies

Spectrophotometric scan of Metformin HCl

The λmax of drug had been determined by subjecting the stock solution (stock 1) to the U.V.

scan between 200-400nm. The wavelength for maximum absorbance was noted from the scan at 233nm (because of sharp and intense peak) in pH 6.8 buffers (blank).

Validation of λmax

The samples containing different concentrations of the drug (2-10µg/ml) were run and overlain spectra describing the reproducibility of the λmax (earlier scanned) was obtained that confiremed and validated the process.

Preparation of standard curve using Ph 6.8 phosphate buffer

Various samples with different concentrations (2, 4, 6, 8 and 10µg/ml) were loaded on UV-vis spectrophotometer and respective absorbances were obtained at λmax 233nm. A graph was plotted (Conc. V/s Absorbance) which resulted a straight line concluding that the drug followed Beer's Lambert's Law at the concentration range of 2-10µg/ml.

The regression analysis was carried out on these experimental data, Y and r2 values were calculated. The obtained values were Y= 0.107x, r^2= 0.975 in 6.8 pH buffer and Y= 0.118x, r^2=0.963 in simulated salivary fluid.

DRUG-EXCIPIENT COMPATIBILITY STUDIES

TLC Studies

The Rf value of Metformin HCl alone and in all drug excipients combinations was found to be nearly thus showed compatibility between drug and different polymers used.

EVALUATION PARAMETERS

Pre compression parameters

Pre-compression parameters like bulk density, tapped density, carr's index, angle of repose and hausner ratio for samples of formulation blend (B_1-B_7) were determined and found in the range of 0.4-0.73, 0.64-0.85, 14-34, 30-44 and 1.22-1.54 respectively.

Post-compression studies

The samples from each batch of tablet formulation were evaluated for post compression parameters such as weight variation, hardness, *In-vitro* dissolution time and percentage drug content. The results inferred weight-variation, hardness, content uniformity and uniformity of dispersion in the range of 849-930, 1.3-1.4, 98-100 and 25-32 respectively.

From the above comparison it was concluded B_3 as the best optimized batch since it gave the highest initial release and later on the final release was also maximum at 30 min time interval.

Thus, finally it is concluded that B_3 is the best optimized batch.

STABILITY STUDY OF OPTIMIZED FORMULATION F_3

The stability studies were performed on prepared formulation at accelerated conditions (30□C±2□C/65%±5% RH) which showed that the formulations suffered no physical changes and also there was no significant reduction in the drug content.

Table No.1: Materials and source

S.No	Material	Source
1	Metformin HCl	Rankem, India
2	PEG-1000	Rankem, India
3	Aspartame	Rankem, India
4	Monoammonium Glycerizinate	Rankem, India
5	Powdered Flavour: Mint and Pine apple	Rankem, India
6	Cremophore RH 40	Rankem, India
7	Talc	Rankem, India
8	D-Maltose	Rankem, India
9	Magnesium Stearate	Rankem, India

Table No.2: Composition of simulated salivary fluid

S.No	Ingredient	Quantity
1	$NaNO_3$	0.01g
2	$MgCl_2$	0.03g
3	$CaCl_2.2H_2O$	0.21g
4	NaCl	0.61g
5	KH_2PO_4	1.63g
6	K_2HPO_4	0.50g
7	KCl	1.00g
8	$NaHCO_3$	0.25g
9	Thimerosol	0.20g
10	Amylase	0.725g
11	Mucin (5%)	2.0ml
12	Antipain 50µg/ml	0.05ml

Table No.3: Formulation design

S.No	Component	B1	B2	B3	B4	B5	B6	B7
1	Drug	500	500	500	500	500	500	500
2	PEG1000	125	100	125	100	125	150	150
3	Talc	100	100	100	100	100	100	100
4	D-Mannitol	100	100	100	100	125	100	125
5	Aspartame	28	28	28	28	28	28	28
6	Monoammonium Glycrizinate	.1	.1	.1	.1	.1	.1	.1
7	Cremophor	14	28	14	28	28	28	28
8	Flavor	14	14	14	14	14	14	14
9	Talc	7	7	7	7	7	7	7
10	Total	888.1	902.1	863.1	877.1	927.1	902.1	927.1

Table No.4: Concentration v/s absorbance data of Metformin HCl

S.No	Concentration (µg/ml)	Absorbance
1	2	0.234
2	4	0.486
3	6	0.698
4	8	0.839
5	10	1.033

Table No.5: Concentration Vs absorbance data of metformin HCl in simulated salivary fluid

S.No	Concentration (µg/ml)	Absorbance
1	2	0.234
2	4	0.496
3	6	0.798
4	8	0.842

Table No.6: Results of pre-compression parameters

S.No	Formulation Code	Bulk Density (gm/ml)	Tapped Density(gm/ml)	Carr's index (%)	Angle of Repose(ɵ)	Hausner Ratio
1	B_1	0.479	0.647	25.96	42	1.35
2	B_2	0.430	0.565	23.89	40	1.31
3	B_3	0.611	0.756	19.18	37	1.23
4	B_4	0.722	0.842	14.25	33	1.16
5	B_5	0.478	0.735	34.96	44	1.53
6	B_6	0.548	0.702	21.93	38	1.28
7	B_7	0.558	0.697	19.94	30	1.24

Table No.7: Post compression data of batch B_1-B_7

Batch	Weight Variation	Hardness	Content of uniformity (% content)	Uniformity of Dispersion (Retained amount %)
B_1	849.2 ±11.49(3.633)	2.1	98.21	99.91
B_2	859.1 ±10.94(3.459)	2.0	99.12	99.9
B_3	869.5 ±17.09(5.404)	2.3	99.40	99.92
B_4	897.8 ±15.86(5.015)	2.1	98.00	99.91
B_5	925.9 ±18.50(5.872)	2.1	99.54	99.92
B_6	910.7±6.44(2.039)	2.1	98.95	99.7
B_7	929.2±2.86(0.904)	2.1	99.12	99.9

***In-vitro* dissolution comparison of formulation B_1-B_4 in pH6.8 phosphate buffer**

Table No.8: Release kinetic data of batch B_1-B_4 in pH 6.8 phosphate buffer

S.No	Time (min.)	Percentage drug release			
		B_1	B_2	B_3	B_4
1	5	35.76	37.62	50.94	37.74
2	10	61.136	59.247	64.02	72.62
3	15	89.385	70.3	82.96	80.42
4	20	92.46	87.709	92.35	84.019
5	25	95.708	92.305	98.03	86.98
6	30	99.243	99.074	99.67	99.822

Table No.9: Release kinetic data of batch B1-B4 in simulated salivary fluid

S.No	Time (min.)	Percentage drug release			
		B_1	B_2	B_3	B_4
1	5	34.96	37.21	50.34	36.86
2	10	60.61	58.73	63.59	72.00
3	15	88.53	69.82	82.36	79.05
4	20	91.62	86.97	91.59	83.91
5	25	95.10	91.95	97.93	86.36
6	30	98.04	98.74	98.92	98.20

Table No.10: Release kinetic data of batch B_3, B_5-B_7

S.No	Time (Mins.)	Percentage drug release			
		B3	B5	B6	B7
1	5	50.94	21.54	22.38	27.00
2	10	64.02	36.71	37.51	41.85
3	15	82.96	47.34	48.81	55.26
4	20	92.35	54.41	53.62	57.72
5	25	98.03	59.49	60.79	64.41
6	30	99.67	60.44	61.34	69.34
7	60	99.68	98.21	99.24	99.81

Table No.11: Release kinetics of B_3, B_5-B_7 in simulated salivary fluid

S.No	Time (Mins.)	Percentage drug release			
		B_3	B_5	B_6	B_7
1	5	50.34	21.23	21.82	26.54
2	10	63.59	35.97	37.13	41.48
3	15	82.36	46.54	48.12	54.64
4	20	91.59	53.98	53.29	56.24
5	25	97.93	58.96	60.73	63.16
6	30	98.92	59.94	61.22	68.21
7	60	99.08	96.21	98.15	98.42

***Ex-vivo* evaluation of B_3 optimized batch**

Table No.12: Release kinetics of B_3 in *ex-vivo* study

S.No	Time	Abs	conc (µg/ml)	conc (mg/ml)	Conc (amt in 15 ml)	Cumulative amount	% release
1	5	0.077	661.9	0.661	9.915	9.9	1.98
2	10	0.364	3128.9	3.128	46.92	47.6	9.51
3	15	1.001	8604.5	8.604	129.06	132.2	26.43
4	20	1.350	11604.6	11.604	174.06	182.7	36.53
5	25	1.714	14733.5	14.733	220.99	232.6	46.51
6	30	0.392	16848.1	16.848	252.72	267.4	53.49
7	60	0.651	27979.9	27.979	419.68	447.7	89.53

Table No.13: Observation of parameters for the stability studies at the accelerated conditions (30^0C $\pm 2^0$ C/65%±5% RH)

S.No	Parameters	Time			
		0 Days	30 Days	60 Days	90 Days
1	Apperence	No change	No change	No change	No change
2	Average weight (mg)	869	869	871	871
3	Hardness (kg/cm^2)	1.4	1.4	1.4	1.4
4	Content of uniformity (%)	99.4	99.4	99.4	99.4
5	Uniformity of drug dispersion (% passed)	99.92	99.92	99.92	99.92

Table No.14: Release kinetic data of optimized batch B3 after 30, 60, 90 days

S.No	Time (in mins)	Percent drug release			
		0 days	30 days	60 days	90 days
1	5	50.94	50.94	50.94	50.94
2	10	64.02	64.02	64.02	64.02
3	15	82.96	82.96	82.96	82.96
4	20	92.35	92.35	92.35	92.35
5	25	98.03	98.03	98.03	98.03
6	30	99.67	99.67	99.67	99.67

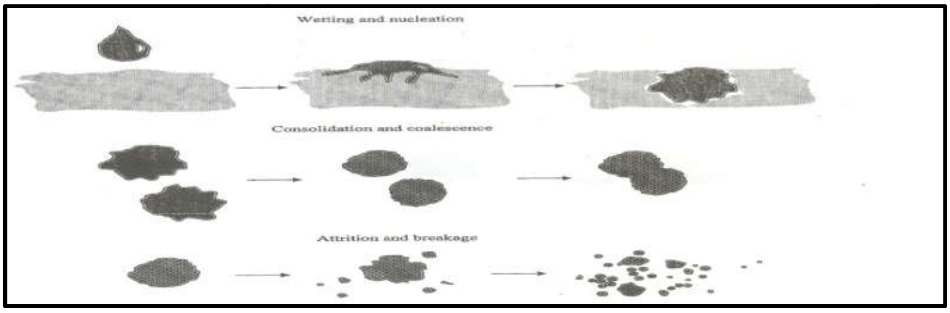


Figure No.1: A recent approach in describing the agglomeration mechanism

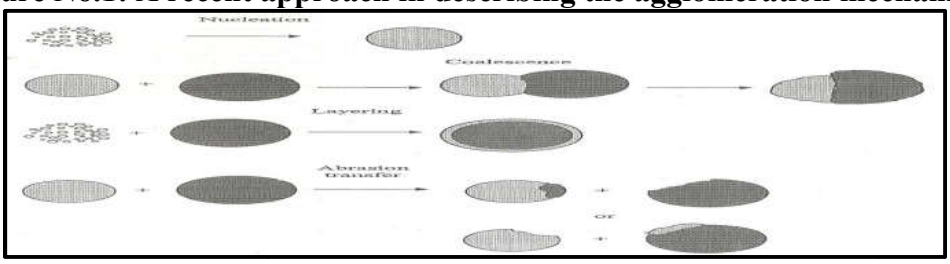


Figure No.2: Elementary agglomerate growth mechanisms

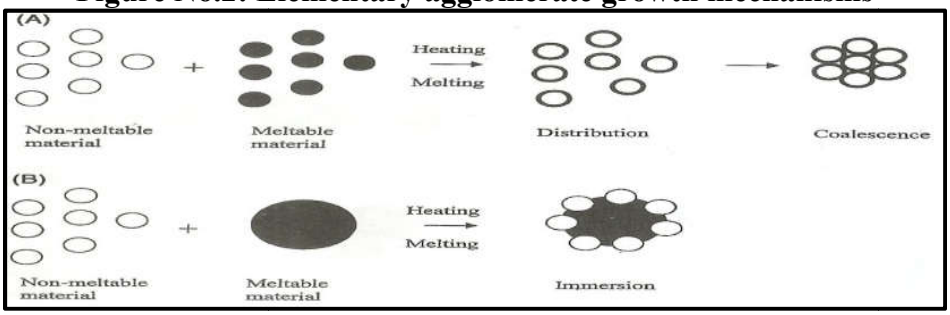


Figure No.3: Modes of nucleation mechanism: (A) distribution and (B) immersion

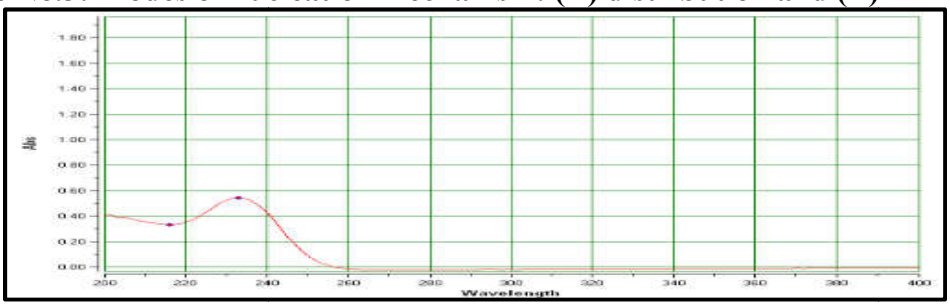


Figure No.4: UV Scan of Metformin HCl showing characteristic wavelength

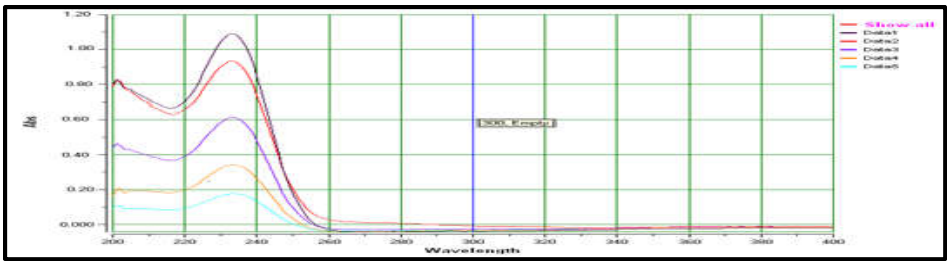


Figure No.5: Overlain spectra of Metformin HCl in pH 6.8 phosphate buffer

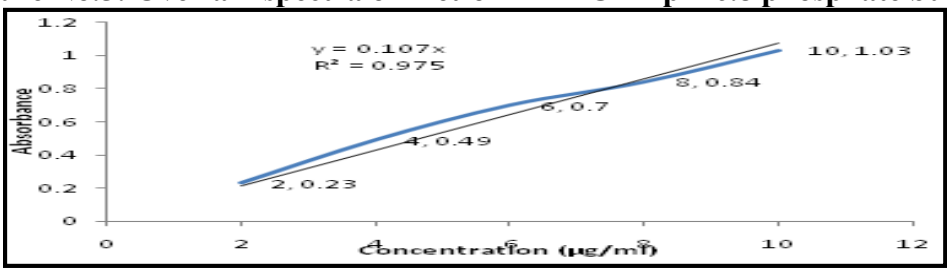


Figure No.6: Standard curve of metformin in pH 6.8 phosphate buffer

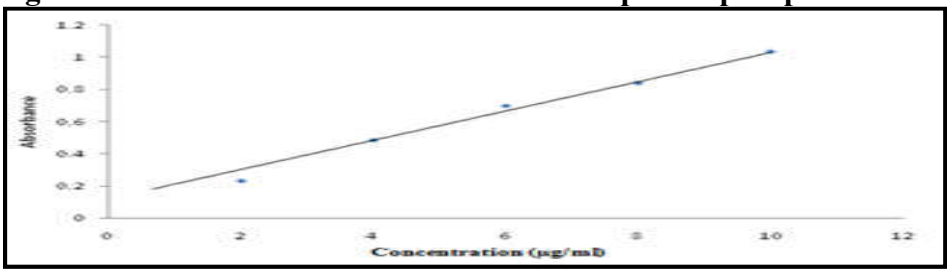


Figure No.7: Standard calibration curve of metformin HCl in simulated salivary fluid

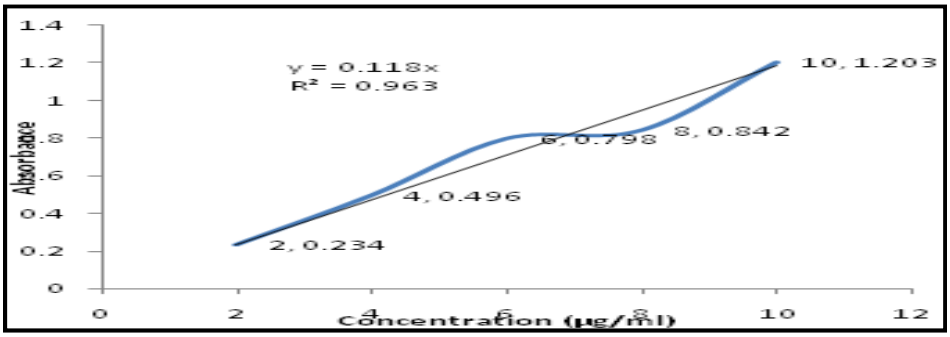


Figure No.8: Regression curve of metformin HCl in simulated salivary fluid

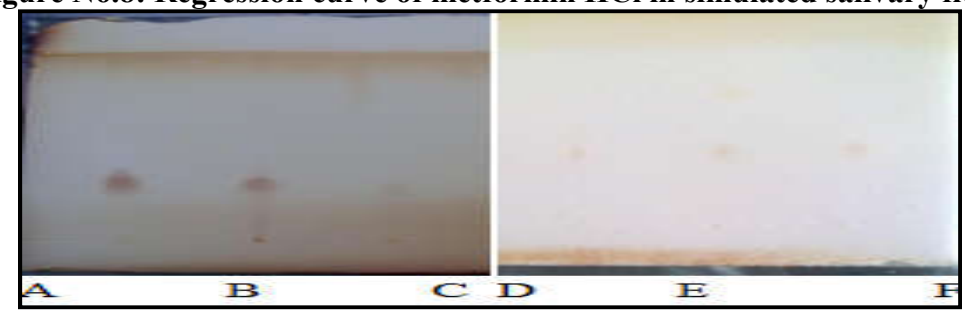


Figure No.9: Compatibility study by thin layer chromatographic method

A: Pure drug, B: Drug with PEG1000, C: Drug with D-Mannitol, PEG 1000, E: Drug with PEG100, D-Mannitol, Chromophore, F: Drug with Talc, Magna sweet, PEG1000

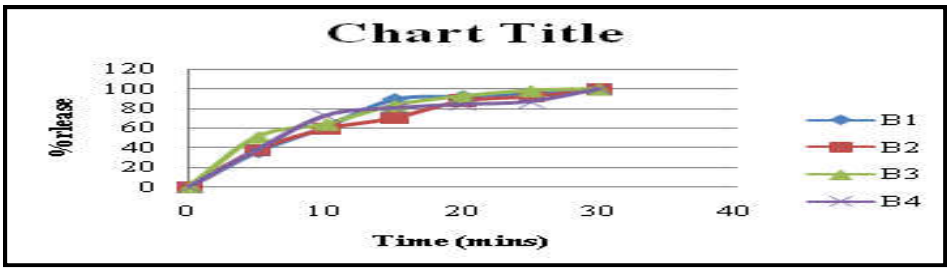


Figure No.10: Comparative release kinetics of batch B1-B4 in pH 6.8 phosphate buffer, *In-vitro* dissolution comparison of formulation B_1 –B_4 in simulated salivary fluid

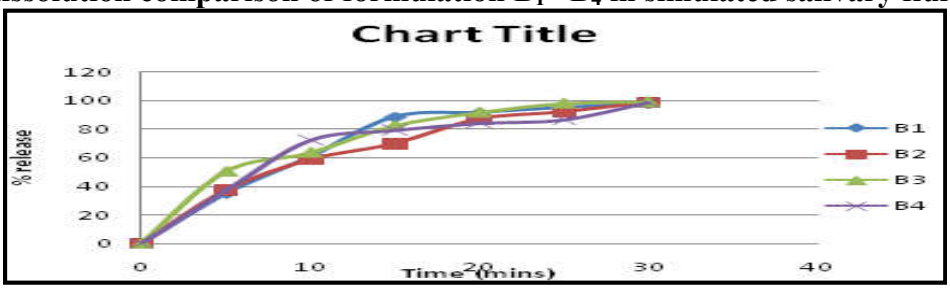


Figure No.11: *In-vitro* dissolution comparison of formulation B_3, B_5-B_7 in pH 6.8 phosphate buffer

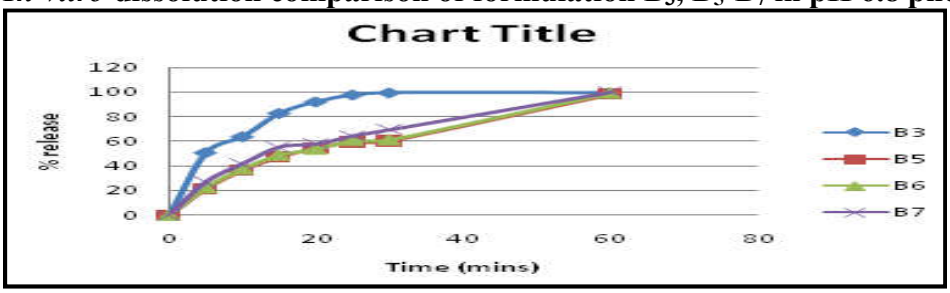


Figure No.12: Comparative release kinetics of batch B_3, B_5-B_7 in pH 6.8 phosphate buffer, *In-vitro* dissolution comparison of formulation B_3, B_5-B_7 in simulated salivary fluid

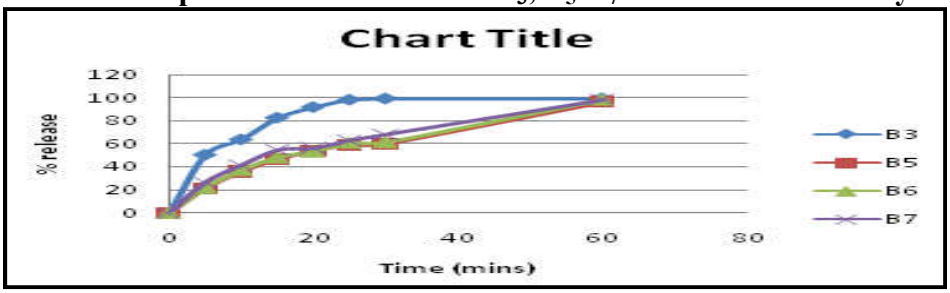


Figure No.13: Comparative dissolution profile of B3, B5-B7 in simulated salivary fluid

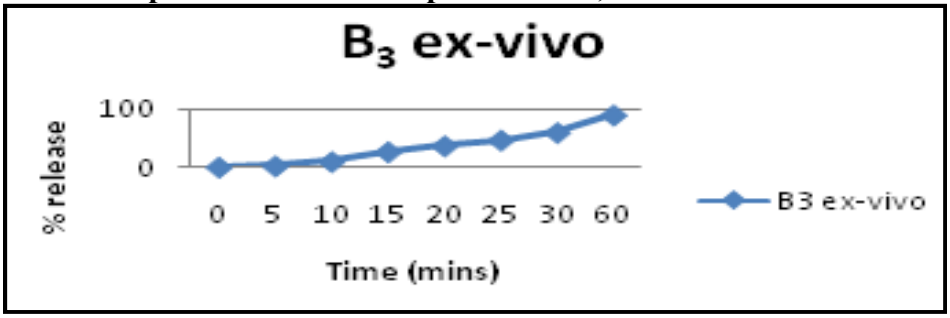


Figure No.14: *Ex-vivo* release kinetics of B_3 in simulated salivary fluid

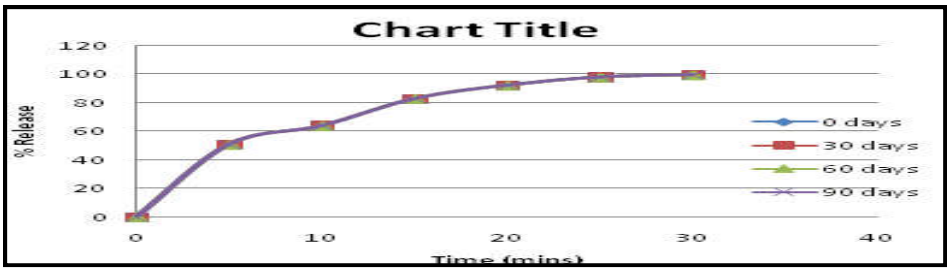


Figure No.15: Release kinetics of B3 in stability testing condition

SUMMARY AND CONCLUSION

The study conducted so far on "Formulation and evaluation of mouth dissolving tablets of Metformin HCl" revealed following conclusions:

By the FTIR study it is confirmed that no interaction took place between the drug and other excipients used in the formulation procedures. The characteristic peaks of the pure drug were compared with that obtained with different blends which nearly same.

The thin layer chromatographs of pure drug and that of different formulation blends confirmed approximately equivalent Rf values. Conclusively metformin HCl was found to be compatible with both polymers and other ingredients incorporated in the formulations.

The Various physicochemical parameters determined with the tablets were bulk density (0.4-0.73g/cc), tapped density (0.64-0.85g/cc), carr's index (14-34%), angle of repose (30-44) and Hausner ratio (1.22-1.54). Other evaluation parameters included in-vitro drug release in buffer systems (98%-100%) and in simulated physiological media (98%-100%).

The *in-vitro* release of the drug with best formulation (B3) in simulated medium was found to be 99.67% which showed fast release over a period of 30 mins.

The stability study was performed with the optimizied formulation (B3) under prescribed conditions which showed that these formulations were stable and thus complied with dose conformity criteria.

Conclusively the present worker reported that such a formulation design could be applied to drugs of various categories which might pave the way to future researchers aiming at optimized pharmacological effectiveness with reduced toxic parameters.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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