RESEARCH ARTICLE

Formulation Development of Sustained Release Matrix Pellets Compressed into Unit Dosage Form

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ABSTRACT

Any drug delivery system's main objective is to consistently deliver the desired drug concentration in the blood or tissues, which is therapeutically beneficial and non-toxic. The spherical, free-flowing granules known as pellets increase bioavailability, lower the risk of dose dumping and local gastrointestinal discomfort, regulate drug release, and boost absorption of the medicine. A second-generation sulfonylurea called gliclazide is used to treat non-insulin-dependent diabetic mellitus (NIDDM). This study's objectives were to construct a flexible dosage form with controlled release and look into how process parameters affected the procedure. To find the batch of pellets that provided a sustained release pattern for the drug gliclazide, several batches of pellets manufactured using the extrusion spheronization process and the design of experiment (DoE) approach were used. Due to their roundness, the pellets had excellent flow characteristics, which affected the dosage production rate. They also had small particles that could be easily dispersed and helped prevent dosing. The release rate of the pellets was 99.3% after 12 hours. With superior medication release control, the study completes the development of sustained-release pellets, minimizing issues with the conventional tablet administration form.

Keywords: Matrix pellet, Gliclazide pellet using DOE, Design of experiment, Extrusion spheronization

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INTRODUCTION

Modified release formulations can be given orally in single-unit dosage or multiple-unit dosage forms. Single-unit formulations contain the active ingredient in a single tablet or capsule, as opposed to multiple-unit dosage forms, which combine several distinct particles into a single dosage unit.[1] These forms include pellets, granules, sugar seeds (non-pareil), mini-tablets, powder, ion exchange resin particles, crystals with pharmaceuticals wrapped around or housed in cores, and crystals with powder as their center.[2] However, multiple-unit dose forms have a variety of advantages over single-unit systems like non-disintegrating tablets or capsules. Both dosage forms have similar drug release profiles. When supplied orally in multiple-unit systems, the subunits of multiple-unit preparations are easily distributed over a large surface area in the gastrointestinal tract. These small particles behave like liquids, quickly leaving the stomach.[3] They can be equally disseminated throughout the digestive tract due to their small size, which may boost bioavailability, lessen toxicity, and have adverse effects while also lowering local drug concentration. Reduced variations in bioavailability across and within individuals, such as those caused by dietary factors.[1-4]

The three categories of pellet applications are food, agricultural, and pharmaceutical. Due to their flexibility in product development, pellets can be made into sustained-release pellets, multi-unit particle systems, and advanced or new drug delivery systems.[5] The active substance in the pellet is gradually dissolved and released by diffusion through its membrane as it travels through the small and large intestines. The active substance and excipients that support its solubility make up the porous core of the pellet.[6,7]

Coated pellets have a quicker transit time than enteric-coated tablets, which can lower the risk of early drug release in the stomach, which could cause drug degradation or gastrointestinal mucosal irritation.[7] The entire medication is split up into numerous units in the multiple-unit system. A system with a few failed units might not be as disastrous as one with one failed unit. This is particularly true of the sustained release unit dose form, in which drug dose dumping can occur.[8] The administration of incompatible medications in a single dosage unit by separating them into distinct multi-particles and mixing multi-particles with various drug release rates to achieve the required overall release profile are additional advantages of this divided dose. A therapeutic agent's release

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Table 1: Formulation trials of gliclazide sustained-release pellets

S. no	*Ingredients*	*B-1*	*B-2*	*B-3*	*B-4*	*B-5*	*B-6*	*B-7*	*B-8*
1.	Gliclazide IP (g)	5	5	5	5	5	5	5	5
2.	PEG 2000 (g)	2	2.5	3	3.5	4	4.5	5	5
3.	MCC IP (g)	20	20	20	20	18.5	18.5	17.5	18.5
5.	Magnesium Stearate IP (g)	0.5	0.5	0.5	0.5	0.2	0.2	0.2	0.2
6.	Talc IP (g)	2.2	1.7	1.2	0.7	2	1.5	2	1
7.	SSG IP (g)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
9.	Millipore Water (mL)	20	12	12	14	12	10	14	14
TOTAL		30	30	30	30	50	30	30	30
SPEED		1500	1500	1500	1500	2000	2000	2000	2000
TIME (Min)		3	5	8	8	8	8	8	8

has repeatedly been postponed via a sustained release in order to retain its plasma profile throughout time and delay or extend its appearance in circulation. Methylcellulose (MCC) is the most often and successfully employed hydrophilic sustained-release material for the fabrication of oral controlled drug delivery systems.[9] The commencement of its pharmacological action is frequently delayed, and the length of the therapeutic impact is sustained.[10] When MCC is exposed to digestive juices, it expands, turns into a gel, and then gradually dissolves. A higher proportion of drug loading has been found to enhance the polymer's swelling rate, dissolution rate, and the corresponding rate of drug release.[11] The physicochemical and biological characteristics of the medication and excipients, as well as how they affect the manufacturing of the dosage form, must be identified and discussed.[12]

The number of persons diagnosed with diabetes globally has skyrocketed during the past 20 years. According to estimates from the World Health Organization (WHO), there were 135 million diabetics in 1995, and 300 million would be affected by the disease by 2025.[13] Here, sustained-release matrix pellets were created using the blood sugar-lowering medication gliclazide, a second-generation sulfonylurea.[14] The liver converts gliclazide and glimepiride into inactive metabolites. The risk of hypoglycemia is related with all sulfonylureas, even though these medications directly stimulate insulin production from pancreatic -cells irrespective of the plasma glucose level.[15] By creating sustained-release gliclazide matrix MUPS, one might investigate better medication combinations while enhancing therapeutic efficacy.

MATERIALS AND METHODS

Materials

Fenofibrate and gliclazide were obtained as gift samples from Indoco Remedies and Ipca Laboratories. The following ingredients were purchased from Research-Lab Fine Chem Industries: microcrystalline cellulose (Avicel PH 101), PEG 2000, talc, mannitol, lactose, povidone, SSG, and magnesium stearate. Eudragit (classes S 100, L 100-55, and RSPO) was received as a kind of gift sample from Evonik Pharma, Mumbai.

Methods

Drug Excipient Compatibility Study

To understand the total influence on product performance during formulation development and during shelf life, drug-excipient interactions are crucial.16 The samples for the compatibility investigations were kept in the open state, parafilm-covered vials with perforations at 40°C and 75 percent relative humidity for 15 days. The samples were a binary mixture of medicine and excipients. The materials were examined visually and examined for physicochemical modifications.

Preparation of Sustained Release Matrix Pellets

The extrusion spheronization procedure was used to create the pellets.[17] Each and every weighted batch of excipients and medication was run through a No. 40 sieve. The medication and excipients were thoroughly blended in a V-cone blender to ensure uniform mixing. Slowly incorporating the batch's optimal medication dosage, the mixture was transformed into a dough (Table 1). The extruder prepared the dough using previously optimized settings. The created extrudates were gathered and put on the checker plate for spheronization. During the optimal period, spheronization was carried out at a predetermined speed. The spheronizer pellets are stored for drying in an air-heated oven at a predetermined temperature (80°C) and duration (60 minutes).

Enteric Coating of Sustained Release Ratrix Pellets by Fluidized Bed Processor

The fluid bed processor (APCG-225) was first filled with 200 g of weighed gliclazide matrix pellets and preheated for 5 minutes. The pellets were then coated with a 3% enteric coating solution made with isopropyl alcohol from Eudragit S 100 and L 100 55 (ratio 1:1) and 5 percent triethyl citrate.[18] There were several variables employed throughout the coating process, including the spray gun nozzle size of 1.22 mm, the atomizing air pressure of 2.5-0.5 kg/cm^2, the intake air temperature of 50–55°C, the product bed temperature of 40–45°C, and the spray rate of 25–50 mL/min. The spray suspension was sprayed to the pellets at a thickness equal to 8.68% (w/w) of the coating load. It took an hour to coat everything. The coated pellets

Table 2: Filler pellets for the compression of matrix gliclazide pellets into tablet

S.no	*Excipient*	*Quantity taken (g)*
1	Mannitol IP 2014	8
2	Povidone IP 2014	2
3	Lactose IP 2014	10
Total		20

were dried for one hour at 50°C bed temperature. To achieve an even size distribution, the pellets were sieved.[19]

Compression of Pellets into a Tablet

The tablet was compressed using a 21 mm x 9 mm die (capsule forming die). Granules were created using acceptable diluents as cushioning fillers in order to punch a tablet, as illustrated in Table 2.[20]

The quantities listed in the table above were precisely weighed, combined, and given enough water in a blender to create a dough. By keeping the dough in an oven at 55°C for 20 minutes, the dough was thoroughly dried. To create the placebo pellets, the dried dough was put through an extruder and a spheronizer[17]

Procedure for compressing tablets: The filler pellets were added to a mixture of 480 mg of sustained-release pellets from batch F8 to increase the weight of the tablet to 800 mg. The pellets were compressed on a single-station tablet press machine (KARNAVATI eng., MINI press).

EVALUATION OF PELLETS

Particle Characterization

Microscopy was used to determine the particle size of different batches of pellets. Under a microscope, the slide containing the microspheres was examined to perform the analysis. The diameter of the pellets served as a measure of their typical particle size.

Microscopy using Scanning Electron Microscope (SEM)

The surface morphology and fractured surfaces were visualized by SEM. The samples were placed on aluminium stand coated with platinum. The samples were analyzed in a non-reactive environment in the absence of air.[21]

Flow Properties

The flowability of the pellets was determined by Carr's Compressibility Index and Hausner Ratio**.** These are measures of the propensity of a powder to be compressed. They were calculated using the formulae [22]

$$\text{Compressibility Index} = 100^* [(V_o - V_t)/ V_o]$$

$$\text{Hausner Ratio} = V_o / V_t$$

Angle of Repose

The static angle of repose was calculated using the fixed funnel and free-standing cone methods. A funnel with its tip 2 cm above a blank sheet of paper was placed on a level, horizontal surface and secured to a retort stand. Until the tip of the cone it had formed was just over the top, the powder was slowly and carefully poured down the funnel. After four measurements, the average base diameter of the powder cone was found, and equation was used to calculate the angle of repose.[22]

$\theta = \tan^{-1} (2h/D)$
h = height of the powder cone
D = diameter of the cone's base

Friability

The combined impacts of abrasion and shock were applied to Ten grams pellets in a friabilator. For 4 minutes, the pellets were vibrated at 100 rpm.[23]

$$\%\text{Friability} = \frac{\text{Initial weight} - \text{final weight}}{\text{Final Weight}} \text{X100 ...}$$

Assay

The crushed pellets had been precisely weighed. The powder, which equates to 80 mg of the gliclazide dosage, was put into a volumetric flask with a capacity of 100 mL. A volumetric flask containing methanol was placed inside a sonicator for 15 minutes. 100 mL were added to the capacity. This solution was filtered, and 1-mL of it was extracted from the filtrate and diluted to 100 mL. This solution's absorbance was calculated and noted. As a result, the assay of the pellets was determined by utilizing a linearity equation deduced from a calibration curve to determine the amount of drug present in the weighed quantity of pellets.

Sieve Analysis

It is employed to ascertain the distribution of aggregate particle sizes within a sample. 16#, 20#, 30#, and 100# sieves were employed, along with a pan at the bottom to catch the fines. The sieve tower was placed in the mechanical shaker and shaken for 10 minutes in ascending order of sieve number (16# at the top and 100# at the bottom). The particles that remained on each sieve after 10 minutes were weighed.[24]
mean was calculated as $d_{mean} = €nd/€n$.
Where n= weight of the powder in grams.
d= mean size in μ
€n= Total weight of the powder.

In-vitro Dissolution Studies

The in vitro release experiments were carried out in a multi-medium with pH 1.2 for the first two hours, pH 4.5 for the third hour, and pH 7.2 for the final hour. On a USP Type II machine, the dissolving media was kept at 37°C and 50 rpm. A UV spectrophotometer operating at 276 nm was used to evaluate the aliquots at various time intervals of 2, 3, 6, 8, and 10 hours.[25]

Evaluation of Compressed Tablets

Pellets may undergo morphological alterations as a result of the compaction of tablets from them, which would significantly alter the product's performance. Therefore, tests such as homogeneity of weight, thickness, hardness, friability, and

Table 3: Observations for drug-excipient compatibility studies

Drug + Excipient	*Ratio*	*Initial appearance*	*Final appearance*	*Assay*
Drug	-	Colorless powder	Colorless powder	97
Drug + Hydroxypropyl methyl cellulose	1:1	Colorless powder	Colorless powder	94.7
Drug A + Lactose	1:1	Colorless powder	Colorless powder	94.3
Drug + Microcrystalline cellulose 1:1		Colorless powder	Colorless powder	95.9
Drug + Magnesium stearate	1:1	Colorless powder	Colorless owder	95.5
Drug + povidone	1:1	Colorless powder	Colorless powder	96.5
Drug + Sodium Starch Glycollate	1:1	Colorless powder	Colorless powder	96.4
Drug + Mannitol	1:1	Colorless Powder	Colorless Powder	96.8
Drug + PEG 2000	1:1	White	White	94.5

in vitro dissolution research were performed on the tablets made from pellets.

Uniformity of Weight

Every tablet in a batch needs to be the same weight, with any weight variance staying within acceptable bounds. The weights were calculated using Sartorious balance to an accuracy of ±1mg. A sample of 20 pills is used to determine weight control.

Thickness

Since thickness has a direct impact on the tablet's hardness, it was evaluated in order to assess homogeneity. Vernier callipers were used to measure the thickness.

Hardness

Using a Hardness testing instrument, diametric compression was used to determine the tablets' hardness (Monsanto Type). A tablet hardness of roughly 4–5 kg is deemed sufficient for mechanical stability.

Friability

In a Roche friabilator, the tablets' friability was evaluated. A sample of 20 tablets or tablets with a known weight (W0) are dedusted in a drum for a set amount of time before being weighted (W) once more. The percentage of friability was determined using the weight loss indicated in the equation below. There shouldn't be more than 1% of weight reduction. Percentage Friablity=W_0-W/W_0*100

Table 4: Flow property, friability, and drug content results of gliclazide matrix pellets pellet

Batch	*Carr's compressibility index*	*Hausner's ratio*	*Friability (%)*	*Drug content*
F1	8.564 ± 0.011	1.080 ± 0.051	0.35 ± 0.014	96.06 ± 0.08
F2	8.226 ± 0.009	1.064 ± 0.052	0.36 ± 0.064	96.59 ± 0.43
F3	6.423 ± 0.013	1.080 ± 0.073	0.40 ± 0.012	95.50 ± 0.34
F4	8.552 ± 0.016	1.085 ± 0.025	0.36 ± 0.1023	97.44 ± 0.25
F5	5.265± 0.025	1.049 ± 0.166	0.37 ± 0.0645	96.04 ± 0.04
F6	6.832 ± 0.036	1.0827 ± 0.381	0.35 ± 0.1832	97.61 ± 0.08
F7	7.432 ± 0.043	1.0927 ± 0.123	0.37 ± 0.0343	96.37 ± 0.04
F8	8.273 ± 0.035	1.0785 ± 0.213	0.38 ± 0.0644	97.17 ± 0.23

All values are expressed as mean ± SD, n=3.

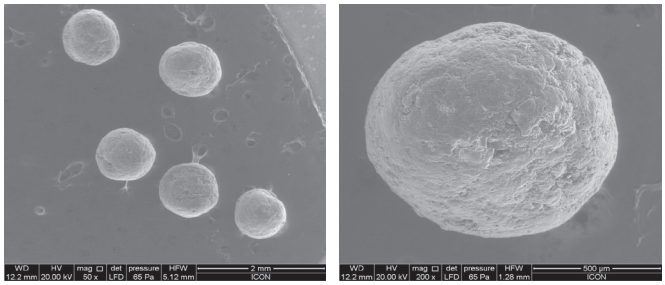

Figure 1: SEM images of pellets at 10X and 100X magnification

In vitro Drug Release Study

The in vitro dissolution investigation was conducted using phosphate buffer (pH 6.8) for the first two hours and 900 mL of 0.1 N HCL for the following two hours. Keep the temperature at 37.5°C. Every hour, aliquots of 10 ml were removed, and an equivalent volume of new dissolving fluid that had reached equilibrium at the same temperature was substituted. Withdrawn aliquots were properly diluted, filtered, and evaluated spectrophotometrically at 276 nm.

RESULTS AND DISCUSSION

Drug Excipient Compatibility Study

From the data derived from physicochemical attributes of the mixtures after 15 days of accelerated conditions, it indicates that all ingredients are compatible with each other means there is no incompatibility of the selected ingredient, as shown in Table 3.

The assay of the binary mixture is well within acceptable limits and reveals the suitability of selected ingredients for formulation development.

Particle Size and Shape

The formulation had a sphere-like shape with an average circumference of 1250–1400 microns, as shown in microscopic analysis. The spherical shape with little drug crystals on the surface was visible in the SEM pictures of the optimized batch P6 (Figure 1). When matrix pellets are drying, this marginal presence is seen. Based on these SEM pictures, the water volume and other processing settings were deemed to be optimal. Dumbbell-shaped pellets may be produced by adding

Table 5: Sieve analysis of optimized formulation (F8)

Sieve no	*Nominal mesh aperture size(μm)*	*Aperture (passed/retained)*	*Mean size opening(μm)*	*Weight powder undersize*	*% weight retained under smaller sieve*	*Weight size Nxd*
16	1000	1000/pan	1000	0	0	0
20	710	710/1000	855	1	1	855
30	600	600/710	655	7	7	4585
100	500	500/600	550	92	92	50600
					(n) =100	(nd)= 56040

Table 6: Results for physicochemical analysis of compressed tablets

Batch	*Hardness*	*Thickness*	*Friability*	*Weight uniformity*	*Disintegration time*	*Drug content*	*CPR*
GT1	4.65 ± 0.39	3.18 mm to 3.76 mm.	0.5751 ± 0.16	495.85 ± 0.47	8.6 Min	96.901 ± 0.68	98.14 ± 0.16

additional water, and broken surface area and friability may increase with higher RPM and temperature.[26]

Flow Properties

The characteristics are reported in Tables 4 and 5, which unambiguously show that the pellets made from MCC-B have appropriate flow qualities. The study's results showed that neither the MCC's crystallinity nor particle size were related to its bulk or tapped characteristics. It is evident that improved packing anticipated from high bulk and tapped densities will result in more water being available on the pellet surface.[27]

Dissolution Studies

Dose dumping is one of the key problems with continuous-release dosage formulations. The most important aspect of dosage dumping in vitro conditions is the amount of active ingredient released at an early stage. The European Medicines Agency (EMEA) mandates that this limit be between 20 and 30 percent.[28] The current research aimed to create an improved bioavailability extended-release pharmaceutical dosage form that would improve patient compliance and release no more than 30% of the total amount of active material in less than two hours. Dissolution tests on the produced pellets demonstrated delayed release behavior. In the first two hours of the optimized batch F8's release of the medicine, NMT 30, 98.2% of the active component was released (Figure 2). The pellets' covered layer remained unharmed. Still, they did somewhat swell during the release procedure. The polymer and coating release ratios have a big impact on the release. It means that the rate-delaying polymers MCC in the core pellets and Eudragit S 100 and L 100 in the coating were used to create prolonged release delivery.[29]

In every instance, "n" in the Korsmeyer-Peppas equation was greater than 0.89. This suggests that the drug was released primarily through a relaxation release process linked to transitions seen in polymers swelling in water. Polymer erosion is another step in this process.[30]

Evaluation of Compressed Tablets

The evaluation of tablets included testing for their hardness, friability, drug content, weight homogeneity, thickness, and in vitro dissolution. The tablets' round shape didn't change, and there were no breaks to be seen. Each tablet displayed a consistent thickness. There was a 3.18 to 3.76 mm thickness range.

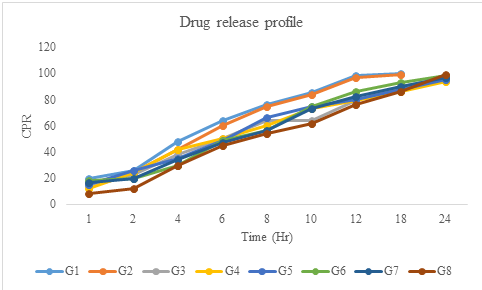

Figure 2: Dissolution profile of Gliclazidematrix pellets

According to official standards, all formulations passed the weight uniformity test because the average percentage deviation of all tablet formulations was found to be within the allowable range. Between several batches of pills, there was noticeable consistency in the amount of medication present, which was greater than 90%. All tablet formulations had a hardness of 4 to 5 kg/cm^2. The firmness of a tablet cannot be determined just by its hardness. Friability is another metric for assessing tablet strength. Conventionally compressed tablets are generally regarded as appropriate if they lose less than 1% of their weight. The percent brittleness in the current study was less than 1% for all formulations, showing that the brittleness was within the permitted limits.[30] Table 6 displays the physicochemical evaluation of compressed tablets.

CONCLUSION

The research proved that MCC and Eudragit S 100 and L 100 were suitable for use in creating pellets for gliclazide. Evaluation of the created pellets showed that process variables, including material mixing and spheronization speed and time, were optimized, producing the best possible product attributes. The tablet that was made from these pellets was stable, easy to handle, and provided gliclazide release over an extended period of time. After disintegration, the divided pellets reduce dose frequency and the possibility of dose drop-off.

DECLARATION OF INTEREST

The authors report no conflicts of interest.

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