

CONTROLLED ORAL DRUG DELIVERY OF HYPOGLYCEMIC AGENT THROUGH PARTICULATE SYSTEM

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ABSTRACT

Gastro retentive systems can be retained in the stomach for a long time so Glipizide hypoglycemic agent used as in gastro retentive formulations in the form of pellets can be developed by using extrusion-spheronization method. Pellets were found to be satisfactory in terms of floatability and drug release behavior. Floatation was achieved during the entire study period of different formulations. The surface morphology of the optimized formulation shows the pellets were smooth and spherical shape. The best formulation was considered to be the optimized one. Improve floating time, sustained drug delivery was observed when the polymer HPMC, HPC, MCC used in the ratio of 28%, 11%, 11%, respectively.

Keywords: Glipizide, Extrusion-Spheronization, Pellets, Polymers HPMC, HPC, MCC

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1.0 INTRODUCTION

The term controlled release implies a system that provides continuous delivery of the drug for a predetermined period with predictable and reproducible kinetics and a known mechanism of release. Also included in this term are systems that provide control over movement of dosage form through the GI tract and / or deliver the drug to a specific area within the GI tract for either local or systemic effect. Among all routes of drug administration that have been explored for the development of controlled-release (CR) systems, the oral route has by far achieved the most attention and success. This is due, in part, to the ease of administration as well as to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes.

Often one encounters additional factors, including the disease being treated, the patient, and length of therapy. Given that it is not practical to alter the physicochemical characteristics of the drug, design of controlled-delivery systems generally optimizes dosage form characteristics relative to the GI environment.

The pattern of motility is however distinct in the two states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the

interdigestive myoelectric cycle or migrating myoelectric cycle (MMC), which is further divided into following four phases¹.

a) Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.

b) Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.

c) Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.

d) Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of two consecutive cycles.

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasting state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate.

A number of drug characteristics need to be considered in evaluating drug candidates for oral CR dosage forms. Some of these characteristics are Dose, Biological Half-Life, Therapeutic range, GI Absorption, Aqueous Solubility, First-Pass Metabolism, Stability to wide pH range, GI enzymes and flora.

Controlled drug delivery systems that can be retained in the stomach for a long time are known as gastro retentive systems. Such retentive systems are important for drugs that are degraded in intestines or for drugs like antacids or certain enzymes that should act locally in the stomach. If the drugs are poorly soluble in the intestine due to alkaline pH, gastric retention may increase solubility before they are emptied, resulting in improved bioavailability. Such systems are advantageous in improving gastrointestinal absorption of drugs with narrow absorption windows as well as for controlling release of the drugs having site specific absorption limitation. Such systems are useful in cases where the drug is best absorbed from the upper part of the intestine².

Drug released from the devices that achieve gastric retention would be emptied along with the gastric contents over a long period and would thus, be present at the main absorption site, the small intestine, for a longer time. This prolonged

gastric retention could improve bioavailability and reduce drug wastage. Therefore, a gastro retentive system will thus, be helpful in achieving maximum effect of the drug³.

Such system cannot be used in case of drugs that induce gastric lesion or for drugs that are unstable in the acidic environment of stomach. Many times drug incorporation is a major problem with such delivery systems^{4, 5, 6}. It is not easy to design and fabricate such systems as retention of these systems depends upon factors such as gastric motility, pH and presence of food^{7, 8, 9, 10, 11, 12, 13}.

2.0 MATERIAL & METHODS

2.1 FORMULATION OF PELLETS

Glipizide pellets were prepared by extrusion-spheronization method. The excipients and drug was mixed to homogeneity (10 min). Isopropyl alcohol/water (9:1) was used as the pelletizing agent and a wet mass of suitable consistency for extrusion was formed. The dampened mass was extruded through a 1.0-mm mesh screen in an extruder at 15 rpm. The extrudates were spheronized for specified time (minutes) at specified rpm in a Caleva model 120 spheronizer. The obtained pellets were dried in a fluidized bed dryer for specified drying time and temperature.

Table 1

Table 1:- Formulation of pellets of different ratio of Drug \ Polymer with water

Formulation of pellets of different ratio of Drug \ Polymer with water.					
Ingredients	Formulations code				
	4A	4B	4C	4D	4E
DRUG	4 Part	4 Part	4 Part	4 Part	4 Part
H.P.M.C	2 Part	2 Part	2 Part	-	-
H.P.C-M	-	2 Part	-	-	2 Part
H.P.C LH-21	-	-	2 Part	2 Part	-
M.C.C	2 Part	-	-	2 Part	2 Part
D \ P ratio	1:1	1:1	1:1	1:1	1:1
Floatability Time(min)	120	105	90	30	90
t 50%	70	80	90	50	40

2.2 Study of the floatation behavior of granules

The floatation studies were carried out to ascertain the floating behavior of various polymer combinations. Static volume Beaker method was initially used to have an idea of the floatation

behavior of the proposed dosage form. A set of formulations were prepared by extrusion-spheronization technique in which the drug along with the polymers were taken. These were then individually placed in separate beakers having equal volume of hydrochloric acid buffer pH 1.2.

Weight of floating pellets

$$\% \text{ floating pellets} = \frac{\text{Weight of floating pellets}}{\text{Initial weight of floating pellets}} \times 100$$

2.3 Bulk density, tapped density and Hausner factor

Granules (1 gm) were placed in a 10 ml volumetric cylinder and their volume was determined. The bulk density was calculated as g/cm³.

The cylinder was then tapped 500 times and the volume was determined again afterward to calculate the tapped density

$$\text{Hausner factor} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

2.4 Particle size distribution

Particle size distribution was determined by sieve analysis. One gram of granules were put on the top of the sieve with a series of openings ranging from 1.41 mm (sieve no. 14), 1.00 mm (sieve no. 18), 0.84 mm (sieve no. 20), 0.41mm (sieve no 40) to 0.20mm (sieve no. 60). The results are reported as percentage of weight retained on each sieve size

2.5 Friability

1 g of pellets were rotated in a Roche friabilator for 10 min, the resulting material were placed on a 250 µm sieve and shaken for 5 min, the amount of material passed through the sieve was weighted and expressed as a percentage

2.6 Moisture content

Moisture content was determined using Mettler PC 440 equipment. A specified amount (1 g) of granules was kept so as to cover the full surface of the pan. The equipment was operated at 105° C for 15 min. After 15 min, the percentage moisture content was recorded from the digital recorder.

2.7 *In vitro* release rate study:-

In vitro dissolution studies were carried out in USP dissolution apparatus II using 900 ml of the dissolution medium [in case simulated gastric condition, hydrochloric acid buffer pH 1.2 was selected] at 37±0.5 °C temperature and at 50 rpm. The 5 ml sample was removed at each predetermined time interval from vessel and the fresh medium was replaced. The samples were filtered using millipore filter assembly and the drug content was estimated by HPLC from the standard area plot of glipizide. For further characterization of delivery system its behavior was also evaluated in simulated intestinal conditions as the study was conducted in phosphate buffer(pH 6.8) following the same dissolution conditions.

2.8 Scanning electron microscopy

The surface morphology of the optimized pellets was seen by scanning electron microscopy (SEM). Scanning electron microscopy was done on a LEO 435 BP instrument. Pellets were fixed on aluminium stubs sputter coated with gold and examined under the microscope

Table 2:- Pellets Characterization of formulations

Pellets Characterization	1A	1B	1C	1D	1E
Bulk Density	0.6	0.58	0.54	0.53	0.50
Tapped Density	0.7	0.67	0.62	0.60	0.57
Compressibility index	14.28	13.4	12.9	11.6	12.28
Hausners ratio	1.16	1.15	1.14	1.13	1.14
Angle of repose	20.4	21.2	19.2	20.1	19.5
Friability %	1.2	1.0	1.2	0.9	0.9
Loss on drying %	1.1	1.2	1.7	2.1	2.5

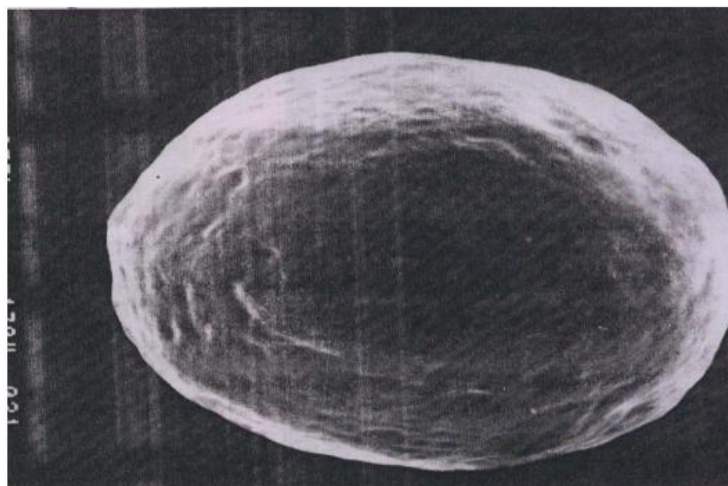


Fig. 1: SEM Photograph of the optimized pellets.

2.9 INFERENCE

The surface morphology of the optimized formulation determined by scanning electron microscopy revealed that the surface of pellets was almost smooth and shape was spherical.

The drug sample was characterized for physical appearance, odour, MP, loss on drying etc. in order to establish the authenticity of the drug.

The drug was identified on UV & FTIR basis. The drug exhibited absorption maxima at 237 nm in the range 200-300 nm which was same as mentioned in literature. On the basis of these studies, it was proved that the drug sample was authentic.

3.0 PROCEDURE FOR FORMULATION OF PELLETS

Excipients and drug was accurately weighed, screened by passing through sieve No. 40 and then admixed in a mortar for 10 minutes. Isopropyl alcohol and water in the ratio of (9:1) was added in sufficient quantity to make wet mass in the following formulation design sets. The wet mass which was subjected to extrusion (at various speeds) to give extrudes which transformed to pellet upon spheronization (at various time and speed of spheronization), were dried at a temperature of 60°C overnight. The various parameters of extrusion and spheronization were needed to optimize on the basis of yield, size and shape and floating tendency.

3.1 PROCEDURE FOR RELEASE CHARACTERISTIC

Weigh accurately the amount of pellets (equivalent to 5.0 mg of glipizide) and placed in a USP type II dissolution vessel, containing 900 ml of dissolution medium, keeping 50 rpm (HCl buffer pH 1.2 or phosphate buffer pH 6.8) and maintaining the dissolution condition as given in USP monograph for glipizide tablet. The sample (5.0ml) was withdrawn from the predetermined intervals from the dissolution vessel. Fresh medium was replaced to keep the volume of medium constant. Sample containing glipizide from HCl buffer pH 1.2 obtained after dissolution were analyzed by HPLC method whereas sample from dissolution studies conducted in phosphate buffer pH 6.8 were analyzed by using the standard plot drawn spectrophotometrically at a wavelength of 275 nm. Dissolution data was reported in cumulative amount dissolved and mean percentage release.

4.0 RESULTS AND DISCUSSIONS

Preformulation studies

Glipizide a potent new sulphonylurea indicated for the control of type II diabetic mellitus acts by partially blocking potassium K⁺ channels in the beta cells of the islets of Langerhans with signaling leading to an increase in intracellular calcium which itself initiate more

insulin release from each beta cell. Glipizide was selected as the model drug for floatable delivery system since it is well absorbed after oral administration with half life of 2-4 hours. It also matched perfectly with this platform as it possesses less density.

The drug sample as received was characterized for its identity, purity and the bulk characterization. Bulk characterization studies of drug involved the measurement of bulk density, tapped density and flow property measurement.

Formulation studies

The floating behavior, drug release, characterization and micromeritic properties were reviewed for selection of excipient having floating capabilities. The design of floating device revealed that the formulation strategy should begin with appraisal of the density function of individual component as it serves a crucial factor which directly affects the floating behavior of the formulation. The density of drug and excipients (polymeric or non polymeric) were considered for the formulation of floating pellets as this would have direct influence on the floating behavior of the formulations. The excipients and drug were so selected to cause this system to float infinitely thus controlling the drug release up to the desired time with minimum variation in the drug concentration level in the blood/plasma.

Optimized formulation

The formulation 7E was prepared using only those fractions of the selected polymers which showed promising floating and release behavior. Only the optimized processing step, conditions were used in preparation of 7E. Table 3 The optimized quantity of granulating fluid i.e. 9:1 (I.P.A: WATER) was selected for the formulation of 7E. The granulated mass was extruded and spheronised at an optimized step of 5, 10, 20 rpm and 500, 1000, 1500 rpm respectively. A yield of 80% was obtained at 5 rpm which however increased to 87% as the speed was raised to 10 rpm, but when the speed was further raised to 20 rpm the yield did not improve. The effect of spheronization on the pellets geometry was studied at two different times i.e. 2 min & 5 min , keeping the speed of spheronization constant i.e. 500, 1000, 1500 rpm. The best step was 500 rpm for 5 min, as a yield of 87 % was observed with minimum wastage of extrudes and also the pellets were spherical in shape at this speed and time combination. However at the same rpm (500) for 2 min partial spheronization was observed. These pellets had comparatively larger size 1000 μm with the 90 % yield but imperfection in shape, size of the pellets was observed .At 1000 rpm, the

extrudes took less time to transform the extrudes into pellets with the product yield of only 75 % and spherical shape of average particle size was only 900 μm . On further increase of spheronization time, pellets become compact agglomerated spheres (made up of 3 -4 pellets) with a size 2000 -2500 μm . The higher rpm (1500) caused the agglomerates to generate powdered particles as it is a surface process where a tangential force is applied throughout extrudes which transform its shape into the spherical pellet. At higher speed frequent scraping was required which would affect the desired spherical shape of the pellets. Hence a balance between spheronization time and spheronization speed would definitely affect the shape and size yield of pellets .So similar justification could be given in case of pellets prepared at 1500 rpm and kept at two different levels of spheronization time. Lower yield (50%) was obtained at 5 minutes whereas 70% yield was obtained at 2 minutes spheronization time. The similar explanation could be given for shape at less and high spheronization time.

The effect of drying time was also studied at two different levels, 6 hr dried pellets was more friable compared to 12 hr dried pellets.

Table 3:- Pellets Characterization of optimized formulations

Formulation code	7E
Bulk Density	0.57
Tapped Density	0.63
Compressibility index	9.5
Hausners ratio	1.10
Angle of repose	19.1
Friability %	0.78
Loss on drying %	1

The drug release characteristic of optimized formulation was studied in phosphate buffer pH 6.8 and much sustained effect was obtained. Applying the various releases modeling predicted that optimized pellets formulation followed release of zero order models in HCl buffer pH 1.2.

The ICH guidelines were followed to carry out the stability testing of drug product. The different evaluation parameters assessed were % weight change (effect of humidity), assay of drug,

specific appraisal parameters for which it was designed (i.e. floating time) and the release characteristic in HCl buffer and phosphate buffer pH 6.8. The pellets were found to be stable.

STABILITY STUDIES OF DRUG – LOADED GRANULES OF GLIPIZIDE

Stability studies were performed to establish the efficacy of the optimized formulations. The effects of storage conditions on the chemical stability of the active drug substances present in the formulations were studied.

Table 23:- Stability assessment of various parameters of formulation (7E)

S.No	Property	Formulation 7E	
		Before stability test	After stability assessment
1	Assay	100.157 (± 0.457)	98.97 (± 0.354)
2	Floating time	420(± 10) minutes	450(± 20) minutes
3	T _{50%}	125(± 15) minutes	130(± 20) minutes

CONCLUSION

The main interest in such a dosage form resulted from its ability to invariably maximize drug absorption by increasing the retention time of the drug in the stomach. Gastroretentive formulations in the form of pellets can be developed by using extrusion-spheronization method. Floation was achieved during the entire study period of formulation 7E. The surface morphology of the optimized formulation 7 E showed that the pellets were smooth and spherical shape. Formulation 7E was considered to be the optimized one. Formulation 7E meets all the desired attributes of a floating drug delivery system.

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