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RESEARCH ARTICLE

Formulation and Evaluation of Floating Matrix Tablets of an Antipsychotic Drug

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ABSTRACT

Dosage forms that can be retained in the stomach are called gastroretentive drug delivery systems (GRDDSs). GRDDS can improve controlled delivery of drugs with an absorption window by continuously releasing the drug for a prolonged period before it reaches its absorption site, thus ensuring optimal bioavailability. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. It is also suitable for local drug delivery to the stomach and proximal small intestines. Gastroretention helps to provide better availability of new products with suitable therapeutic activity and substantial benefits for patients. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamics advantages of CR-DFs of these drugs. In the present study, Ziprasidone was selected as model drug in the design as GFDDS using various lipoidal/ fatty polymers. Ziprasidone complies with all the requirements that are suitable for a drug candidate to be formulated as GFDDS, as it has specific site of absorption in upper part of GIT. Since the half-life of Ziprasidone is 2 h, the optimized polymer with best floating and retarding ability, that is, Gelucire 43/01 is subjected to aging studies to assess the effect of ageing by differential scanning calorimetry. Hence, it is evident that the non-effervescent gastro retentive floating multi-unit formulations of Ziprasidone is feasible and may be manufactured with reproducible characteristics with the aid of Gelucire 43/01 as polymer.

Keywords: Floating Matrix Tablets, Antipsychotic Drug, GRDDS

INTRODUCTION

Gastroretentive drug delivery systems (GRDDSs)

Dosage forms (DFs) that can be retained in the stomach are called GRDDS. GRDDS can improve controlled delivery of drugs with an absorption window by continuously releasing the drug for a prolonged period before it reaches its absorption site, thus ensuring optimal bioavailability. Drugs with an arrow absorption window are mostly associated with improved absorption at the jejunum and ileum due to the enhanced absorption properties of these sites (e.g., large surface area), or due to enhanced solubility in the stomach as opposed to the more distal parts of the GIT [Figure 1].

Anatomy and physiology of the stomach

The stomach is situated in the left upper part of the abdominal cavity under the diaphragm, between the lower end of the esophagus and the small intestine, and is the most dilated part of the GIT. Its opening to the duodenum is controlled by the pyloric sphincter. The stomach can be divided into four anatomical regions, namely fundus, body,

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Table 1: Salient features of upper gastrointestinal tract

Section	Length (m)	Transit time (h)	pH	Microbial count	Absorbing surface area (m2)	Absorption pathway
Stomach	0.2	Variable	1–4	<103	0.1	P, C, A
Small Intestine	6–10	3±1	5–7.5	103–1010	120–200	P, C, A, F, I, E, CM

P-Passive diffusion, C-Aqueous channel transport, A-Active transport, F-Facilitated transport, I-Ion-pair transport, E-Entero-or pinocytosis, CM-Carrier mediated transport

Table 2: Time transit in each segment of the GI Tract

Segment	Type of food	
	Liquid	Solid
Stomach	10–30 min	1–3 h
Duodenum	<60 s	<60 s
Jejunum and ileum	3±1.5 h	4±1.5 h

Table 3: Different HPMC grades (Methocel) and their properties (Colorcon, Asia ltd)

Viscosity	Molecular weight of various grades of HPMC (Methocel)			
	A	E	K	F
3		7000		
5		10000		
15	16000	17000	16000	17000
50	18000	20000	19000	19000
100	26000	28000	27000	27000
400	41000	44000	42000	43000
1500	63000	68000	65000	66000
4000	86000	92000	88000	90000
10000	104000	113000	108000	109000
15000	120000	131000	125000	127000
100000	208000	225000	215000	218000

Grade	Number of Molecular Units
A	186
E	201
K	192
F	195

antrum, and pylorus. Gastric volume is important for dissolution of do sage forms *in vivo*. The mean capacity of the stomach is 30 mL at birth, IL at puberty and >1.5–2L in adults. Gastric pH affects the absorption of drugs from controlled release (CR) DFs. There is a large volume difference in gastric secretion in normal and achlorohydric individuals. It affects *in vivo* dissolution of drugs when administered with 180 mL of water. The pH of the stomach in fasted condition is about 1.2–2.0 and 3–6.5 in the fed condition. In general, basic drugs will have a better chance of dissolving in the

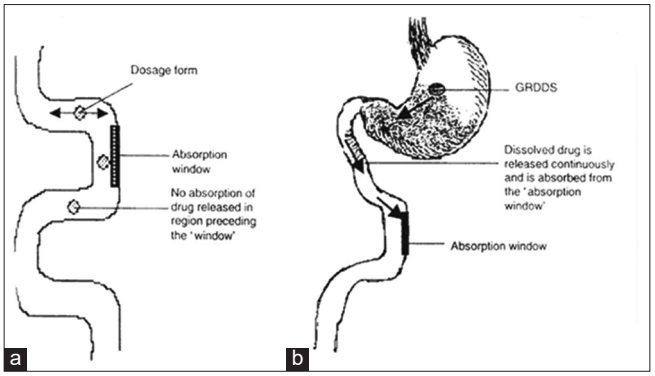

Figure 1: Drug absorption in (a) conventional dosage forms and (b) gastroretentive drug delivery systems

fed condition than in the fasted condition. Food buffers neutralize gastric acid, thus increasing the pH up to about 6.5 [Tables 1 and 2]. After complete ingestion of a meal, the pH rapidly falls back to below 5.0 and then gradually declines to the fasting state values over a period of time [Figure 2a and b].

Progress in controlled gastroretentive delivery systems

Oral CR DFs have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance, and flexibility in formulation. However, this approach is be dilled with several physiological difficulties such as inability to restrain and locate the controlled DDS within the desired region of the gastrointestinal tract (GIT) due to variable gastric emptying and motility. Furthermore, the relatively brief gastric emptying time in humans which normally averages 2–3 h through the major absorption zone, that is, stomach and upper part of the intestine can result in incomplete drug release from the DDS, leading to reduced efficacy of the administered dose. Therefore, control of placement of a DDS in a specific region of the GI tract offers advantages

for a variety of important drugs characterized by a narrow absorption window in the GIT or drugs with a stability problem.[1]

These considerations have led to the development of a unique oral CR dosage form with gastro retentive properties.[2] After oral administration, such a DF, would be retained in the stomach and release the drug there in a controlled and prolonged manner so that the drug could be supplied continuously to its absorption sites in the upper GIT.[3] Gastroretentive DFs can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. It is also suitable for local drug delivery to the stomach and proximal small intestines.[1] Gastroretention helps to provide better availability of new products with suitable therapeutic activity and substantial benefits for patients. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamics advantages of CR-DFs of these drugs [Table 3].

METHODS AND MATERIALS [TABLES 4 AND 5]

Tables 4 and 5.

RESULTS AND DISCUSSION

In the present study, Ziprasidone was selected as model drug in the design as GFDDS using various lipoidal/fatty polymers. Ziprasidone complies with all the requirements that are suitable for a drug candidate to be formulated as GFDDS, as it has specific site of absorption in upper part of GIT. Since the half-life of Ziprasidone is 2 h, multiple doses are needed to maintain plasma concentration for a good therapeutic response and improved patient compliance.

GFDDS of Ziprasidone was developed, to avoid fluctuations in the plasma drug concentrations as well as for increasing bioavailability of Ziprasidone. The GFDDS retains in the stomach and there by improves the bioavailability of drugs that have an absorption window in a particular region of the GI tract than conventional oral controlled delivery systems.

Table 4: Materials used in the work

S. NO	MATERIALS	VENDOR
1	ZIPRASIDONE	A Generous gift from Dr REDDY'S Laboratories, Hyderabad
2	GELUCIRE 43/01	A Generous gift from GATTEFOSSE Corp, France
3	HPMCK100M	A Generous gift from ISP Hong Kong Pvt Ltd., Hyderabad.
4	HPMCK4M	A Generous gift from ISP Hong Kong Pvt Ltd., Hyderabad
5	COMPRITOL 888ATO	A Generous gift from Shashan Pharmaceuticals Pvt Ltd., Pondicherry
6	PRECIROLATO 5	A Generous gift from Shashan Pharmaceuticals Pvt Ltd., Pondicherry
7	LUBRITAB	A Generous gift from Aurabindo Pharma Pvt Ltd., Hyderabad
8	CREMOPHOR	A Generous gift from Aurabindo Pharma Pvt Ltd., Hyderabad

Table 5: Equipments used in the Work

S. No.	EQUIPMENT	MANUFACTURER	MODEL NO
1	Electronic single pan balance	Shimadzu	GP3202
2	Dissolution apparatus	LabIndia	Disso2000
3	UV spectrophotometer	Cyberlab	3220 UV
4	IR spectrophotometer	Nicolet	5700
5	DSC	Breeze	DSCQ1000
6	Heating Mantle	Biotechniques, India	BTIL
7	Hot Pan	Remi Equipments	1MLH
8	Flask Shaker	Kemi	KRS2
9	Hotairoven	Dolphin	75177
10	Mesh#16,40	Jayant	ASL00

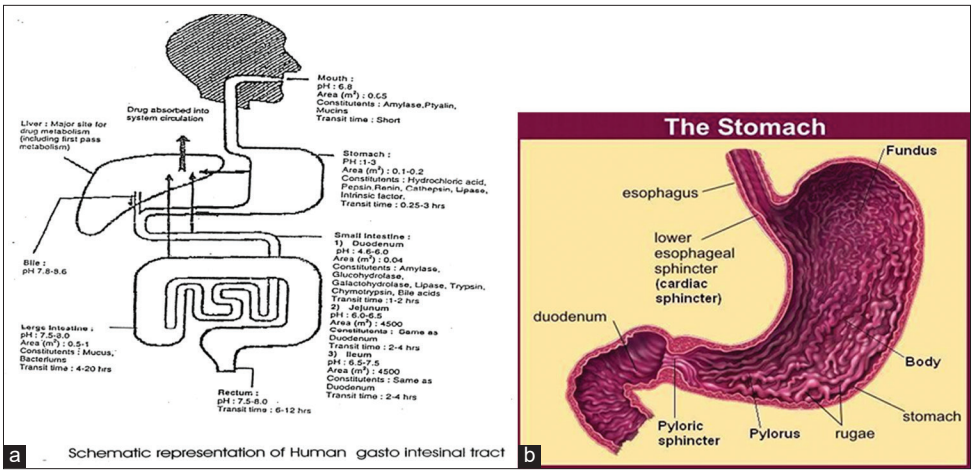

Figure 2: (a) Schematic representation of Human Gastrointestinal tract (b) Schematic illustration of the stomach anatomical structure

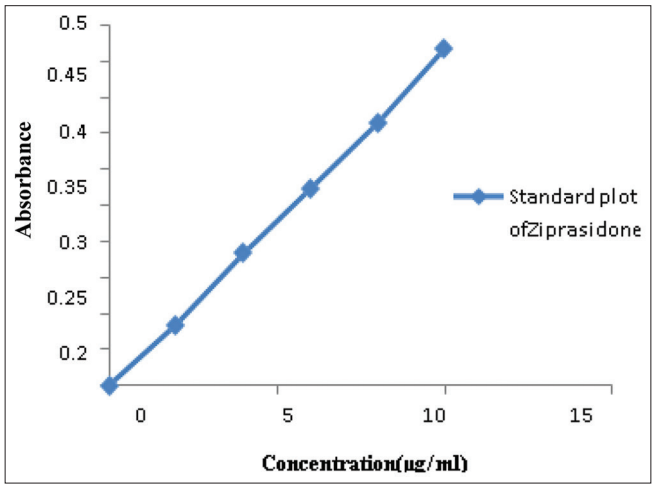

Figure 3: Standard Plot of Ziprasidone at 318 nm

Table 6: Standard Plot Values of Ziprasidone at 318 nm

CONCENTRATION (µg/ml)	ABSORBANCE
0	0
2	0.084
4	0.183
6	0.273
8	0.364
10	0.468

Standard plot of ziprasidone

The standard graph of Ziprasidone in 0.1 NHCl showed a good linearity with R^2 of 0.9993, in the concentration range of 2–10 µg/ml.

The pharmaceutical compositions are designed as multi-units, to be more suitable, because they claim to reduce the inter subject variability in absorption and lower the probability of dose dumping.

Ziprasidone and controlled matrix polymer granules were prepared by different granulation techniques in the ratio of 1:1, 1:1.5, and 1:2 [Figure 3].

Ziprasidone multi-unit formulations with drug and polymer proportion as 1:1, F1, and F2 formulations consisting Cellulose polymers HPMC K4M and HPMC K100, respectively, were prepared by wet granulation technique [Table 6].

Ziprasidone multi-unit formulations with drug and polymer proportion as 1:1, F3, F4, F5, F6, and F7 formulations consisting lipoidal/fatty polymers, that is, Compritol 888 ATO, Precirol ATO 5, Lubritab, Cremophor EL, and Gelucire 43/01 were prepared by melt granulation technique [Tables 7-9].

The drug content estimated was found to be with in the specified limits, that is, less than ± 5% variation of the stated amount of Ziprasidone. All the multi-unit granule GFDDS were evaluated for the physical parameters such as Bulk density, Tapped density, Compressibility Index, Hausner ratio, and Angle of repose.[4-6]

Granules comprising cellulose polymers has shown good flow properties, whereas granules comprising lipoidal polymers has shown results inferior to that of cellulose polymers as they are prepared by melt granulation technique, but is passable.

The entire prepared multi-unit granule GFFDS were subjected to *in vitro* buoyancy studies that are carried out in 0.1 N HCl. All the formulations F1–F21 were tested for floating parameters such as floating lag time and floating duration time.[7-30]

Table 7: Assay values of the prepared formulations

Formulation	Drug Content (%)
F1	98.23
F2	99.65
F3	99.12
F4	98.44
F5	99.23
F6	98.63
F7	99.65
F8	98.65
F9	98.45
F10	99.64
F11	98.12
F12	99.72
F13	97.13
F14	99.12
F15	98.45
F16	98.65
F17	99.43
F18	97.67
F19	98.56
F20	99.51
F21	99.43

Table 8: Physical parameters of the prepared formulations

Formulation	CI	Angle of repose	Hausner ratio
F1	12.3	20.6°	1.14
F2	15.9	23.5°	1.18
F3	18.8	31.2°	1.23
F4	17.7	30.7°	1.38
F5	19.4	26.8°	1.24
F6	18.2	33.1°	1.23
F7	18.6	32.8°	1.32
F8	12.5	20.9°	1.16
F9	18.9	24.2°	1.15
F10	18.1	31.7°	1.27
F11	17.5	31.2°	1.38
F12	19.5	30.8°	1.24
F13	18.3	27.6°	1.35
F14	18.9	32.8°	1.36
F1c85	12.1	21.3°	1.14
F16	15.7	24.8°	1.15
F17	18.4	32.1°	1.28
F18	17.9	32.5°	1.36
F19	18.6	31.4°	1.26
F20	19.4	36.2°	1.33
F21	19.1	33.7°	1.36

Formulations prepared with cellulose polymers in different drug to polymer proportions (F1, F2,F8, F9, F15, and F16) had shown buoyancy lag time which might be the time taken for hydrogel formation, whereas all the other formulations prepared with lipoidal polymers in different drug to polymer proportions had floated from zero time. However, in case of multi-unit, formulations prepared with Compritol 888 ATO and Precirol ATO 5 10–20% and 60% of granules, respectively, had shrinked to the bottom after 2 h. Other multi-unit GFDDS prepared with Lubritab, Cremophor, and Gelucire43/01 had shown excellent buoyancy characteristics beyond 12 h of study.

Table 9: *In vitro* buoyancy results of prepared formulations

Formula	Buoyancy Lag Time (Min)	Duration of Floating (Hrs)
F1	20 min	>12
F2	35 min	>12
F3	---	>12 (10–20%) ↓
F4	---	2 (60%) ↓
F5	---	>12
F6	---	>12
F7	---	>12
F8	25 min	>12
F9	42 min	>12
F10	---	>12 (10–20%) ↓
F11	---	2 (60%) ↓
F12	---	>12
F13	---	>128
F14	---	>12
F15	28 min	>12
F16	43 min	>12
F17	---	>12 (10–20%) ↓
F18	---	2 (60%) ↓
F19	---	>12
F20	---	>12
F21	---	>12

↓-shrinkage

CONCLUSION

Oral drug administration is by far the most preferable route for taking medications. However, the therapeutic window of many drugs is limited by their short circulating half-life and absorption through a defined segment of the GIT. Such pharmacokinetic limitations may lead in many cases to frequent dosing of these medications to achieve the required therapeutic effect and hence poor patient compliance.

Majority of drugs are having site specific absorption in the gastro intestinal tract and parameters such as pH dependent solubility, stability, and ionization of the drug in different portions of the G.I. tract, influence such absorption. Gastric retention time is one of the important factors, which adversely affect the absorption of drugs when administered simply by an oral controlled delivery system.

Gastro retentive FDDS possess the ability of being retained in the stomach and help in optimizing the oral controlled delivery of drugs having absorption window by continuously releasing drug for prolonged period of time thus ensuring optimal biological absorption.

Many attempts have been made in recent years to provide a DFs with longer gastric retention time and therefore a more efficient absorption. Floating DDS is well proved and documented to be therapeutically superior to conventional dosage system in number of studies.

Hence, the aim was "in accordance with the therapeutic objective, to design, and to evaluate hydrodynamically balanced non-effervescent Floating DDS s of Ziprasidone as CR modules," which prolongs the release rate of the drug while extending the residence time of the drug with in the body environment and without causing undeliterious effects to the subject.

The present work was carried with an in house experimental design to prepare multi-unit granule GFDDS employing successful cellulose polymers and various efficient lipoidal/fatty polymers with a motto to optimize best polymer among all of them for formulation of hydrodynamically balanced floating DDS of Ziprasidone.

Ziprasidone multi-unit granule GFDDS with controlled matrix cellulose and lipoidal polymers were prepared by different granulation techniques in the ratio of 1:1, 1:1.5, and 1:2.

Ziprasidone multi-unit formulations comprising cellulose polymers were prepared by wet granulation technique, whereas the Ziprasidone multi-unit formulations comprising lipoidal/fatty polymers were prepared by melt granulation technique.

All the multi-unit granule formulations (F1 to F21) prepared were evaluated for drug content and all the formulations had shown good results within the official limits. They are even assessed for flow characteristics such as bulk density, tapped density, Carr's index, and Hausner ratio. Formulations with cellulose polymers had shown excellent flow characters, whereas formulations prepared employing lipoidal polymers had shown a bit inferior results to cellulose polymers as they are prepared by melt granulation, but are passable.

The entire prepared multi-unit granule GFFDS were subjected to *in vitro* buoyancy studies that are carried out in 0.1 N HCl. All the formulations F1–F21 were tested for floating parameters such as floating lag time and floating duration time. Formulations prepared with cellulose polymers in different drug to polymer proportions (F1, F2, F8, F9, F15, and F16) had shown buoyancy lag time which might be the time taken for hydrogel formation, whereas all the other formulations prepared with lipoidal polymers in different drug to polymer proportions had floated from zero time. However, in case of multi-unit, formulations prepared with Compritol 888 ATO and Precirol ATO 5 10–20% and 60% of granules, respectively, had shrinked to the bottom after 2 h.

The *in vitro* drug release studies of the entire prepared multi-unit GFDDS were studied separately according to their proportions (1:1, 1:1.5, and 1:2) using 0.1 N HCl as medium in USP XXIV paddle type dissolution apparatus.

Assessment of dissolution study results revealed that formulations F7 (Ziprasidone: Gelucire 43/01–1:1), F10 (Ziprasidone: Compritol 888 ATO–1:1.5) and F19 (Ziprasidone: Lubritab-1:2) had retarded the drug release in controlled manner up to 12 h. Hence, these formulations were considered as promising formulations.

Even though formulation F10 employing Compritol 888 ATO had retarded the drug release up to 12 h, due to its poor buoyancy characteristics, some extent of granules had shrinked, which is not desirable for a GFDDS. Formulation F19 prepared with Lubritab as controlled floating polymer had retarded the drug release up to 12 h successfully, but at a high drug to polymer concentration of 1:2. Formulation F7 prepared with low concentration of Gelucire (1:1 proportion) had retarded the release

of Ziprasidone in a rate controlled manner up to desired 12 h. Since the formulation F7 utilized less polymer concentration, it was considered as the best optimized formulation among other formulations.

The optimized formulation F7 was evaluated for its floating ability and *in vitro* drug release studies against single unit GFDDS prepared employing same polymer, that is, Gelucire 43/01 with drug to polymer ratio of 1:3. By comparing the buoyant characteristics and release characteristics among F7 and single unit, single unit GFDDS had shown excellent floating ability for more than 12 h, also the drug release was found to be 81% for 12 h, by an unknown mechanism of drug release.

The dissolution characteristics of optimized multi-unit formulation F7 are compared with that of the pure drug and Marketed formulation (Zeldox). Pure drug had shown its high hydrophilic characteristics by releasing 93% of drug in 0.5 h itself, whereas Ziprasidone marketed formulation Zeldox had shown drug release of more than 97% in 1 h.

To establish the mechanism of drug release, the experimental data were fitted to five popular exponential equations. The drug release of Ziprasidone prepared from cellulose polymers (by wet granulation) and from the Lipoidal/fatty polymers (by melt granulation) followed zero-order kinetics which were clearly indicated by higher "r" values of zero-order release when compared to those of first-order release model. The relative contributions of drug diffusion and matrix erosion to drug release were further confirmed by subjecting the dissolution data to Higuchi model and Erosion model. It was found that all the formulations followed diffusion mechanism as indicated by their higher "r" values. By fitting all the data into Korsemeyer pappas model (Power Law), all the formulations had shown exponent "n" values above 1 indicating the drug release strictly followed zero-order super case II transport as the drug release mechanism.

Compatibility among the drug and optimized polymer, that is, Gelucire 43/01 was assessed by performing IR spectroscopy studies and Differential Scanning Calorimetry (DSC) Studies. It was concluded that that there was no interaction between the drug and polymer as the principle peaks of the drug were found unaltered in the IR spectra. No prominent enthalpy changes were observed in the DSC thermograms of Ziprasidone+Gelucire 43/01 physical mixtures and optimized formulations on comparison with the peaks of drug and polymer alone, which may considered that Ziprasidone and Gelucire are compatible enough without any interactions.

The optimized polymer with best floating and retarding ability, that is, Gelucire 43/01 is subjected to ageing studies to assess the effect of ageing by DSC.

Hence, it is evident that the non-effervescent gastroretentive floating multi-unit formulations of Ziprasidone is feasible and may be manufactured with reproducible characteristics with the aid of Gelucire 43/01 as polymer. In conclusion, very promising *in vitro* results were observed with multi-unit floating formulations of Ziprasidone.

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