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Research

Effect of an Effervescent Agent on Various Characteristics of Repaglinide Floating Tablets

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Abstract

Formulation of repaglinide floating tablets is the purpose of the work that is being done at the moment. Over the course of the experiment, varying doses of sodium bicarbonate, which is a gas-generating agent, were combined with varying amounts of retardation polymers. There were several grades of Methocel polymers that were utilised as retarding polymers. These grades included Methocel K4M, K15M, and K100M. After conducting an analysis of the formulation blend for a number of different physicochemical properties, it was discovered that all of the parameters were within acceptable ranges. Several different quality control criteria were tested after the formulations F1 through F9 were developed and evaluated. Every single formulation was successful in passing the tests, and the outcomes were within acceptable parameters. Based on the dissolution data, it was clear that formulation F8 was the most effective, with a maximum percentage of drug release of 98.73% and a floating time of 12 hours.

Keywords: Repaglinide, floating tablets, Methocel, sodium carbonate.

INTRODUCTION

Oral directions of medication administration have a high level of recognition, accounting for between 50-60% of all entire dosage forms[1]. When compared to the maternal route, oral drug delivery, which includes the administration of medications in the form of tablets, capsules, powders, emulsions, suspensions, and other similar substances, is regarded as the most prevalent, most popular, convenient, and safe method[2]. The simplicity of administration, exact dosage, self-medication, pain avoidance, and most significantly, patient compliance are the primary reasons for the increased popularity of solid dosage forms[3]. Tablets and capsules make up the vast majority of the solid dosage forms that are authorised for use. However, one of the most significant disadvantages of solid dosage forms is that solids, in particular, are not suggested for use with patients who are unconscious,

paediatrics, or elderly[4]. The application of gastrointestinal physiology provides a greater degree of versatility in the formulation of dose forms compared to the prevalence of other routes.

As a result of the low cost of therapy and the ease of administration, which leads to high levels of patient compliance, the oral route continues to be the preferred method for the administration of therapeutic substances. The conventional oral dosage forms are able to deliver a particular concentration of the medicine into the systemic circulation, but they do not allow any control over the distribution of the drug[5].

The controlled-release drug delivery systems, also known as CDDS, are responsible for delivering drugs at a rate that is preset, predictable, and under control. Repaglinide is a drug that was developed in 1983 and belongs to the class of drugs known as meglitinides. It is used to treat diabetes. In patients with type 2 diabetes mellitus, repaglinide is a medicine that is taken orally and is used in conjunction with diet and exercise to regulate blood sugar levels[6]. The mechanism of action of repaglinide involves the stimulation of insulin release from the β-islet cells of the pancreas. Similar to other anti-diabetic medications, hypoglycemia is a primary problem that should be brought to the attention of the medical community[7]. The secretion of insulin from the pancreas is stimulated by repaglinide, which results in a reduction in blood glucose levels. In order to accomplish this, it closes potassium channels in the membrane of the beta cells that are dependent on ATP supply. This causes the beta cells to become depolarised, which opens the calcium channels in the cells[8].

The calcium influx that occurs as a result of this causes insulin to be secreted. Because of its short half-life (one hour), dosage frequency (two to four times a day), and local action in the stomach, repaglinide is an excellent choice for a floating drug delivery system[9-10].

MATERIALS AND METHODS

Materials

Sun Pharmaceutical Industries Ltd., Mumbai provided me with a free sample of Repaglinide as a sample of their product. Drugs India Mahaveeray in Hyderabad was the source of the various grades of Methocel that were purchased. Bicarbonate sodium was acquired from Sri Laxmi Chemicals, which is located in Hyderabad. We obtained MCC from Vishnupriya Chemicals Private Limited, which is located in Hyderabad. The magnesium stearate was purchased from Sisco Research Laboratories Pvt. Ltd. in Hyderabad, while rest of the chemicals and reagents were purchased from SD Fine Chemicals in Hyderabd area.

Methods

Optimization of sodium bicarbonate concentration

Sodium bicarbonate was utilised as the ingredient that was responsible for producing effervescent gas. Floating the formulation is made easier by this. A number of different concentrations of sodium bicarbonate were utilised, and both the effervescent floating lag time and the effervescent floating duration were measured through observation. The concentration of sodium bicarbonate was determined to be finalised and then proceeded with for additional formulations based on this information[11].

Table 1: Optimization sodium bicarbonate concentration

Sl. No.	Name (mg)	EF1	EF2	EF3
1	Repaglinide	2	2	2
2	Methocel K4 M	10	10	10
3	$NaHCO_3$	5	10	15
4	Mg. Stearate	3	3	3
5	Talc	3	3	3
6	MCC PH 102	q.s.	q.s	q.s.

Table 2: Composition of effervescent floating tablets of repaglinide using different concentrations of polymers

Formulation code (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Repaglinide	2	2	2	2	2	2	2	2	2
Methocel K 4M	5	10	15	-	-	-	-	-	-
Methocel K 15M	-	-	-	5	10	15	-	-	-
Methocel K 100M	-	-	-	-	-	-	5	10	15
$NaHCO_3$	10	10	10	10	10	10	10	10	10
Magnesium Stearate	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3

MCC PH 102	37	32	27	37	32	27	37	32	27
Total weight	60	60	60	60	60	60	60	60	60

Pre-compression characteristics

Mixing the numerous substances that were described allowed for the development of powder blends, which were then utilised for the purpose of characterising the flow qualities of powder. Flow properties done by bulk density**,** tapped density, compressibility index and hausner's ratios[12].

Calibration curve of repaglinide

The establishment of a standard calibration curve for repaglinide was the first step in the research project. To construct the standard graph of repaglinide with 0.1N hydrochloric acid (HCl), concentrations ranging from 0.2 µg/ml to 1 µg/ml were used on the X-axis, and absorbance values were shown on the Y-axis.[12-13]

Preparation of repaglinide floating matrix tablets

The preparation of effervescent floating matrix tablets of repaglinide by the use of Methocel K 4M, Methocel K 15M, and Methocel K 100M was accomplished through direct compression method. Following the precise weighing of each component, the mixture was filtered through a mesh size of sixty. Microcrystalline cellulose, sodium bicarbonate, talc, and magnesium stearate were each mixed individually after the medication and polymer were first blended geometrically in a mortar and pestle for fifteen minutes. This was done in order to ensure that the remaining components were thoroughly combined. After these components had been completely combined, the powder mixture was next filtered through a mesh size of forty. The tablets were compressed using the direct compression method using a multi punch 8 station Rotary tablet compression machine (Cadmach, Machineries Ltd., Lab press 8 stations, India). The punches used were 6mm flat round punches[14].

Post compression characteristics

A number of physicochemical parameters, including weight variation, hardness, thickness, friability, and drug content, were investigated in relation to the tablets that were designed for the formulation[15].

Drug release kinetics

Through the utilisation of the correlation coefficient (R2), it is able to assess the degree to which each model is good at fitting the data[16].

RESULTS AND DISCUSSION

Calibration curve of repaglinide

The standard curve of repaglinide was obtained in 0.1N HCl at 245 nm with a good correlation was obtained with R^2 value 0f 0.998[17].

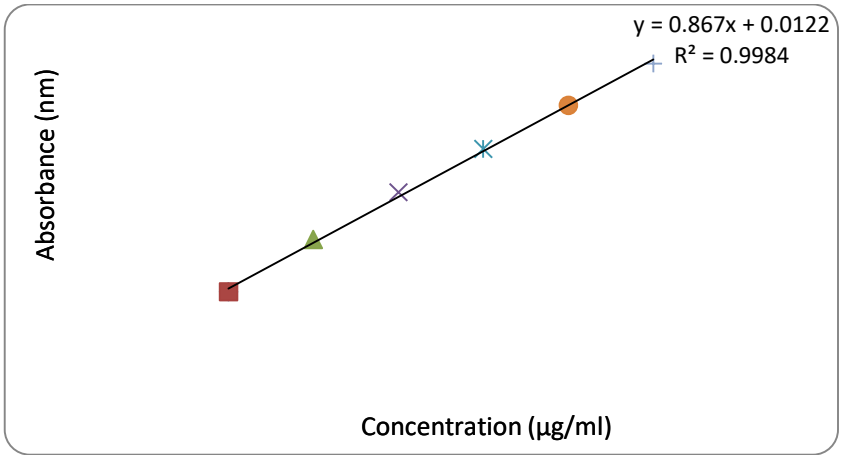

Fig 1: Calibration curve of repaglinide

Pre-compression characteristics

It was discovered that the bulk density of all of the formulations fell within the range of 0.51 to 0.55 g/cm^3, indicating that the powder possesses favourable flow qualities. Upon examination, it was discovered that the tapped density of each of the formulations fell within the range of 0.52 to 0.55, indicating that the powder possesses favourable flow qualities. It was discovered that the compressibility index of all of the formulations fell somewhere in the range of 15 to 17, which indicates that the powder possesses favourable flow performance. All of the formulations have demonstrated that the hausner ratio falls within the range of 0.97 to 1.21, which indicates that the powder possesses favourable flow qualities.

Table 3: Micrometric properties of powder blend

Formulation Code	Bulk density	Tapped density	Compressibility Index	Hausner's ratio
F1	0.51	0.53	16.22	0.97
F2	0.53	0.54	15.12	0.98
F3	0.54	0.55	16.39	0.94
F4	0.55	0.52	15.10	1.03
F5	0.54	0.53	15.72	1.14
F6	0.55	0.54	16.29	1.16
F7	0.53	0.55	15.87	0.99
F8	0.52	0.54	15.20	1.18
F9	0.54	0.55	15.05	1.21

Post compression characteristics

Following the determination of the physical features of Repaglinide floating tablets (F1 to F9), which included weight fluctuation, thickness, hardness, friability, and drug content, the results of the formulations (F1 to F9) were found to be within the limitations stated in official books. Specifications for thickness and diameter can be established on an individual product basis if applicable. When there is an excessive amount of variance in the thickness of the tablet, it can lead to issues with the packaging as well as acceptability among customers. It may be concluded that the powders behave in a consistent manner throughout the compression process because there is no discernible variation in the thickness of the tablets within any formulation. It was discovered that the thickness of the tablets of each and every formulation fell somewhere in the range of 2.1 to 2.6 mm. The variation in tablet density and porosity is reflected in the degree to which tablets differ in their hardness. Tablets were discovered to have a hardness rate that fell anywhere between 1.7 and 1.9 kg/cm^2. It was discovered that the percentage of friability of each and every formulation fell somewhere in the range of 0.51% to 0.56%.This shows that the tablets that have been manufactured have a good handling characteristic. The tablet weighs approximately 60 mg on average. When it comes to percentage deviation, the pharmacopoeial limit is ±5% alone. All of the tablets had weights that ranged from 57 mg to 65 mg. In terms of drug content, all of the floating tablet formulations have demonstrated a high degree of homogeneity, and they contain between 97.04 and 99.61% of repaglinide, which is within the limit that was stipulated.

Table 4: Evaluations of physical parameters of tablets

Formulation Code	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Drug content (%)	Floating lag time (sec)	Floating buoyancy time (h.)
F1	59	2.6	1.8	0.51	97.79	102	12
F2	61	2.1	1.7	0.52	98.39	99	11
F3	58	2.2	1.9	0.54	97.04	108	12
F4	60	2.3	1.8	0.55	99.61	103	12
F5	62	2.2	1.8	0.55	97.39	104	12
F6	57	2.3	1.9	0.56	99.08	102	11
F7	65	2.5	1.9	0.53	97.62	98	12
F8	64	2.3	1.8	0.55	98.42	104	12
F9	60	2.4	1.8	0.54	98.79	106	11

A method that is effervescent was chosen because it is capable of providing buoyancy *in vitro.* As an agent that generates gas, sodium bicarbonate was added to the mixture. The formation of carbon dioxide occurred

as a consequence of the interaction between the acidic fluid and sodium bicarbonate, which occurred as the dissolving medium (0.1N HCl) was absorbed into the tablet matrix. Due to the fact that the gas that was created was encased and protected within the polymer, the density of the tablet was effectively reduced. It became buoyant once the tablet's density decreased below 1, which caused it to become buoyant. In order to prevent the dosage form from travelling into the small intestine along with food, the system should float within a few minutes of coming into touch with stomach fluid. The floating lag time was less than 108 seconds for all of the formulations, ranging from F1 to F9.

The *in vitro* dissolution studies of floating tablets of repaglinide were conducted in simulated gastric fluid 0.1N HCl for 12 hours and *in vitro* drug release data shown in figure 2, 3 and 4.

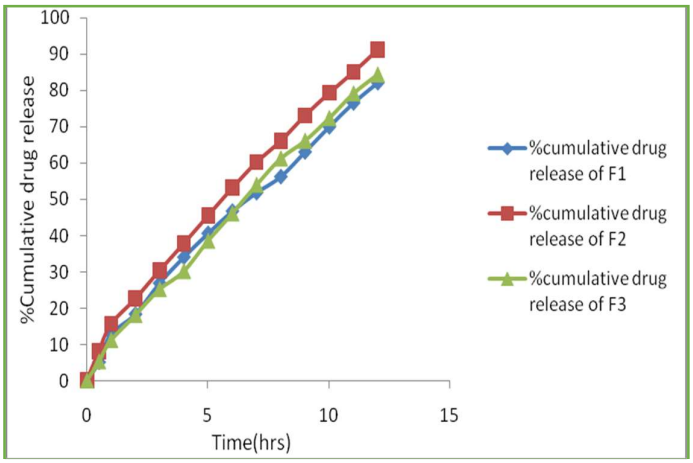

Fig 2: Percentage drug release of formulation (F1-F3)

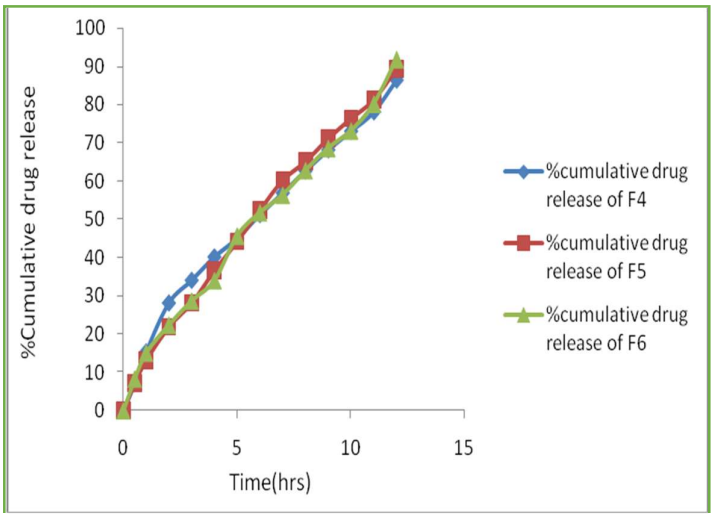

Fig 3: Percentage drug release of formulation (F4-F6)

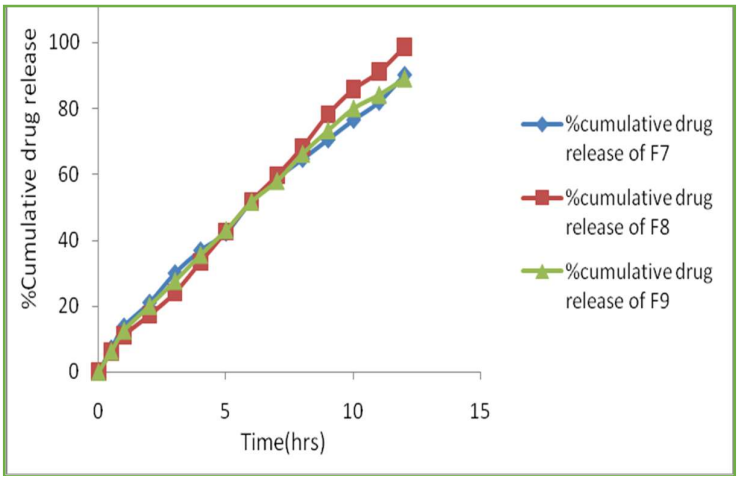

Fig 4: Percentage drug release of formulation (F7-F9)

Because of the causes that led to its status as the best formulation, Formulation F8 was able to achieve the intended drug release profile with a percentage of 98.73%.

For the purpose of determining which model provides the greatest fit and gaining an understanding of the release behaviour of the formulation, the release kinetics of the optimised formulation (F8) have been assessed using a variety of models. Zero order, first order, Higuchi, and Korsmeyer-Peppas are some of the models that have been tried and tested. It is possible to evaluate the goodness-of-fit of each model by utilising the correlation coefficient (R^2), and the optimised model demonstrated the zero order release kinetics.

Table 5: Mechanism of drug release kinetics of optimized formulation (F8)

Release kinetics model (R^2 values)	**Zero Order**	**First Order**	**Higuchi**	**Korsmeyer peppas**
Optimized formulation (F8)	0.998	0.930	0.915	0.846

CONCLUSION

Repaglinide tablets' floating ability was greatly enhanced by adding the effervescent ingredient. The floating periods of tablets containing effervescent agents were significantly longer than those of tablets without these additives. The release of repaglinide from tablets containing effervescent agents was more regulated and maintained. By reducing the likelihood of sharp swings, this may help with maintaining stable blood glucose levels. In most cases, adding effervescent agents kept the tablets' physical integrity and hardness intact. To keep the tablet from dissolving too quickly or losing its mechanical strength, the ideal concentration of the effervescent agent must be maintained. The research found the sweet spot for effervescent agent concentrations that allowed for both floating and effective drug release. If the drug's floating duration or release kinetics is out of the appropriate range, it could have a negative impact on both. Adding effervescent chemicals to repaglinide floating tablets improves their drug release profile and floating features, which could lead to better pharmacokinetic qualities and better diabetes management.

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