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Original Research Paper

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DESIGN AND EVALUATION OF GASTRO-RETENTIVE FLOATING TABLET OF SITAGLIPTIN

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ABSTRACT The present study of Sitagliptin Floating tablets were to develop optimized gastric floating drug delivery system (GFDDS) by using the polymers HPMC K4M and Carbopol 940 to enhance the bioavailability and therapeutic efficacy of Sitagliptin. Various approaches have been followed to encourage gastric retention of an oral dosage form. Floating systems have low bulk density so that they can float on the gastric juice in the stomach. In the present work attempts have been made to prepare Sitagliptin Floating tablets by Direct compression method, 4 formulations (F1 to F4) floating tablets of Sitagliptin were prepared using variable concentrations of HPMCK4M and Carbopol940,buoyancy lag time and the total floating time was studied for all the formulations. FT-IR Studies shown that polymers are compatible with each other and there was no interaction found between polymer and drug.

KEYWORDS : Floating drug delivery system (FDDS), HPMC, Carbopol, Sitagliptin, in-vitro release

INTRODUCTION

As compared to other routes for drug administration, oral route is the most preferred as it is much convenient. Therefore more research has been focused on controlled release oral drug delivery systems, but the important difficulty is associated in designing the controlled delivery systems for better absorption and enhanced bioavailability. In case of conventional oral delivery systems the dosage forms passes through the stomach and small intestine within very short period of time decreasing bioavailability and to increase bioavailability dosage forms have to stay inside the stomach or upper intestine for desired period of time so that entire drug can be released from the dosage forms. Gastro retentive systems retain the dosage forms for several hours inside the stomach increasing gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. The controlled gastric retention solid dosage forms have been developed by means of various mechanisms such as of mucoadhesion,**1** flotation,2 sedimentation,**3** expansion,**4** modified shape systems,**5** or by the simultaneous administration of pharmacological agents,6 that delay gastric emptying. Among the above different techniques Floating drug delivery systems (FDDS) **7** are novel drug delivery systems. Where the solid dosage forms remain buoyant condition on the gastric fluid and release the drug slowly and gastric residence time can be enhanced significantly. This is a very simple but highly innovative concept. More over it has several advantages over other gastro retentive drug delivery systems. Sitagliptin phosphate is a drug used to treat diabetes mellitus. It is incompletely absorbed from the gastrointestinal tract and has an oral bioavailability of only 85% while remaining drug is excreted unchanged in feces. This is because of poor absorption in lower gastrointestinal tract. Therefore, the formulation of Sitagliptin phosphate as a gastro-retentive floating drug delivery system was thought to be beneficial, to improve bioavailability.

MATERIALS &METHODS:

Sitagliptin phosphate (Gifted sample from Glenmark Pharm, India), HPMC, Carbopol, Sodium bicarbonate, MCC, Citric acid and other chemicals of analytical grade.

Methodology of the experiment:

Two different polymers hydroxypropylmethyl cellulose (HPMC K4M**)** and carbopol were mixed in different ratio to obtain a suitable matrix system for achieving the extended release profile of the drug Sitagliptin. In order to optimize the ratio of HPMC K4 M & carbopol for matrix system used in extended release tablet formulation, different batch is prepared by trial and error method.

Table No1: Composition of different tablet formulations

Components (mg)	F1	F2	F3	F4
Drug	100	100	100	100
HPMC K4	125	100	150	200
Carbopol	150	200	125	100
NaHCO3	50	50	50	50
Citric acid	25	25	25	25
MCC	135	135	135	135
Mg-Stearate	5	5	5	5
talc	10	10	10	10
Total weight of Tablet:	600	600	600	600

At first all ingredients (HPMC K4M, carbopol, Drug, MCC, NaHCO3, citric acid) were mixed by geometric dilution. Then Granules are prepared by 16 mesh and subsequently followed by 24 mesh sieve. After that the granules are subjected to drying in hot air oven until 5% moisture retains. After optimum drying the prepared granules are ready for punch in tablet punching machine.

EVALUATION OF FORMULATIONS:

Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations.

Hardness Testing:

The resistance of tablet for shipping or breakage, under conditions of storage, transportation and handling, before usage, depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester [8].

Thickness testing of formulated tablets:

Thickness of tablets was important for uniformity of tablet size. Thickness was measured using Vernier Calipers on 3 randomly selected samples [8].

Weight Variation Test of final formulation:

The USP weight variation test is run by weighing 20 tablets individually, calculating the average weight & comparing the individuals tablet weight to the average. The tablets meets the USP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

Weight Variation tolerance for uncoated tablets according to USP 9.

Friability Test:

Friability is the measure of tablet strength. Roche friabilator was used for testing the friability using the following formula.

$$\%\text{Friability} = \frac{(\text{Initial wt. of tablets} - \text{Final wt. of tablets}) \times 100}{\text{Initial wt. of tablets}}$$

Buoyancy / Floating Test:

The time between introduction of dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT). The lag time was carried out in beaker containing 250 ml of 0.1N HCl (pH 1.2) as a testing medium maintained at 37°C 11.

DISSOLUTION STUDY:

Apparatus: Dissolution test apparatus (USP XXIII)
Method: USP type 2 apparatus (paddle)
Dissolution medium: 0.1N HCl + 0.5% SLS
Volume of DM: 900 ml
Temperature: 37 + 0.5 C
Speed: 50 rpm

Procedure:

The tablet was placed inside the dissolution vessel. 10 ml of sample were withdrawn at time intervals of 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12hr. The volume of dissolution fluid adjusted to 900 ml by replacing 10ml of dissolution medium after every sample. Each sample was analyzed at 267nm using double beam UV and Visible Spectrophotometer against reagent blank. The drug concentration was calculated using standard calibration curve 12.

RESULT:

The powder mixtures of all the formulations were tested by various studies including, bulk density (ranging from 0.35 to 0.45 gm/ml), tapped density (ranging from 0.40 to 0.48 gm/ml), Carr's index (ranging from 6.18 to 12.58%) and Hausner's ratio (ranging from 1.06 to 1.14). All the results showed moderate flow property

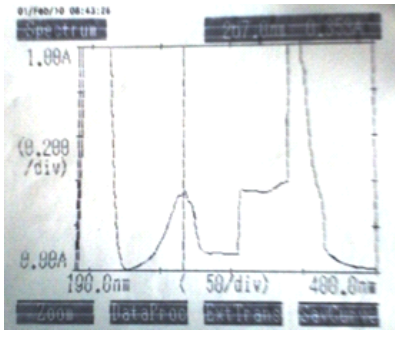

Figure 1: Absorbance peak of Sitagliptin at 267 nm.

Table No 2: Micromeritic properties of tablet formulation Mean ± SD

Batch Code	Bulk Density (gm/ml)	Tap Density	Hausner's Ratio	Carr's Index
F1	0.38 ± 0.015	0.43± 0.017	1.14± 0.03	12.38± 2.52
F2	0.45± 0.011	0.48± 0.005	1.06± 0.04	6.18± 3.48
F3	0.42± 0.011	0.45± 0.020	1.08± 0.07	7.22± 6.54
F4	0.35± 0.015	0.40± 0.005	1.14± 0.06	12.58± 4.25

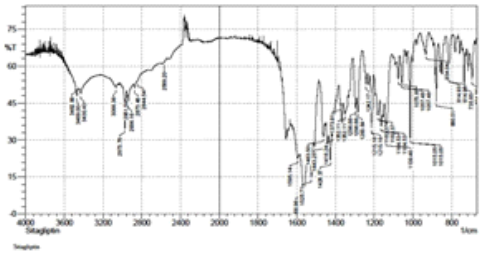

Figure 2: FT-IR Spectra of Sitagliptin phosphate.

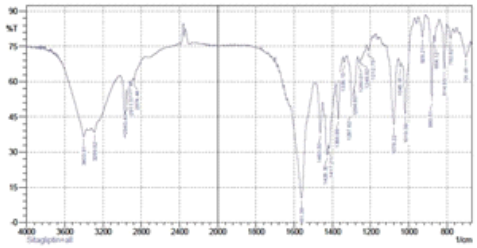

Figure 3: IR spectra of Sitagliptin Phosphate and polymer

All the IR peaks present in pure drug are also present in final formulation in the same region. So, it is concluded that there is no chemical interaction between drug & polymer.

Table No 3: physicochemical characterizations of formulated tablets.

Batch Code	Hardness (kg/ Sq. Cm) [Mean ± SD]	Thickness (mm) [Mean ± SD]	Friability Test [Mean ± SD]	% of weight variation	Floating lag time (sec) [Mean ± SD]	Duration of floating (hr) [Mean ± SD]
F1	5.17± 0.15	5.14 ± 0.03	0.95 ± 0.19	98.72	24.33± 0.58	11.27± 0.25
F2	6.33 ± 0.21	4.02± 0.08	0.33± 0.16	100.28	43.33± 1.53	13.67± 0.29
F3	5.9 ± 0.35	4.43± 0.10	0.84± 0. 00	98.83	31.67 ± 2.08	12.33± 0.29
F4	5.4 ± 0.10	4.77± 0.12	0.55± 0.25	99.83	29.00± 1.00	10.67± 0.29

The results of physicochemical characterizations are given in table. The evaluated properties showed good results for further studies. The effect of hardness on buoyancy lag time was studied and results indicated that with increasing the hardness lag time also increased.

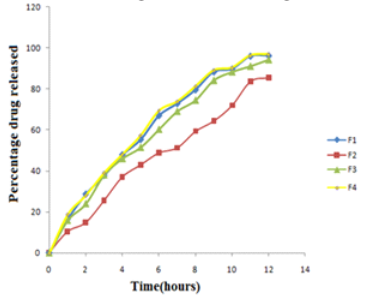

Figure 4: In Vitro Drug Release Profile of all formulations

The in vitro dissolution study shows that the floating tablets are capable of drug release over a period of 12 hours. The study shows that the floating tablets absorbed the water and got swollen. Initially a barrier gel layer forms around the tablet and the interior of the tablet remains dry. The drug diffuses through this barrier gel layer gradually erodes with time and release the drug. The dissolution data are treated and analyzed to understand the kinetic and mechanism of the drug release from the floating matrix tablet. The treated data are fitted into various kinetic models and R2 value are evaluated (Table). The analysis shows that the drug release from the floating matrix followed Higuchi release kinetics more preferably. As the "n" (release exponent) values of Krosmeyer-Pappes model of most of the formulation batch are in the range of 0.72 – 0.88. So, the release mechanism is non-fickian leading to gradual erosion of matrix.

CONCLUSION:

A floating extended release formulation of a antidiabetic drug sitagliptin have been prepared by a unique blend of polymer (HPMC) and carbopol matrix, NaHCO3 (Sodium bicarbonate) and

other excepients in an optimized ratio to achieve an extended or delayed drug release profile upto around 12 hours. There is no physical and chemical interaction occurs between drug (sitagliptin) & other excipients during the formulation process. It is supported by FTIR analysis. NaHCO3 (Sodium bicarbonate) is used in the tablet formulation as a floating agent. NaHCO3 helps to retain the tablet dosage form by maintaining an optimized floating lag time (FLT) & total floating time (TFT) in the stomach, without disturbing the drug release profile.

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