International Journal of Enhanced Research in Science, Technology & Engineering
ISSN: 2319-7463, Vol. 12 Issue 3, March-2023, Impact Factor: 7.957

Analysis of the Improved Formulation's Gastroretentive and in Vivo Pharmacokinetic Properties

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ABSTRACT

The GIT absorbs very few pharmacological compounds equally and fully. Slow-release preparations of medications that are absorbed in the stomach, duodenum, and small intestine (GIT) reach lower areas, where their absorption is decreased prior to their full release. Creating a controlled release dosage form with a longer stomach retention period can boost the bioavailability of medications with a particular absorption window. Recent methods to extend the drug delivery system's stomach residency period include (1) bioadhesive devices (36–38) and (2) smaller, quickly growing systems. (3) low-density gastric floating system. These dose forms deliver the medication into the upper portions of the small intestine and stomach Known as angiotensin II (AG II) receptor antagonists, losartan potassium is a class I anti-hypertensive medication used to treat hypertension. Losartan potassium is well absorbed, with a half-life of 1.5 to 2.5 hours, and a systemic bioavailability of roughly 33%. Therefore, the absorption of Losartan potassium controlled release dose form will be increased by an extended stomach retention period. Therefore, in order to increase its oral bioavailability, losartan potassium is seen as a good option for the construction of a gastric floating drug delivery system. In order to extend the duration of drug release and give the sustained release tablet formulations floating properties, an attempt has been made to formulate GRDDS of Losartan potassium using hydroxy propyl methyl cellulose of various viscosity grades (HPMC K4M, HPMC K15M) and polymers such as carbopol 934P and sodium alginate.

Keyword: Pharmacological, Bioavailability, Bioadhesive, Medications

INTRODUCTION

The GIT is a 9-meter-long tube that runs from the mouth to the anus in the center of the body. Pharynx, esophagus, stomach, duodenum, jejunum, and ileum in the small intestine, and cecum, appendix, colon, and rectum in the large intestine, comprise the GIT. From the esophagus to the anus, the GIT's general anatomy is the same, however each area has some minor differences. The stomach is a large, muscular sac-like organ located underneath the liver and diaphragm in the left upper portion of the abdominal cavity. The stomach wall resembles the other sections of the digestive tube, but it contains an additional oblique layer of smooth muscle inside the circular layer that facilitates the intricate grinding movements. Physical digestion (churning movement), chemical digestion, and absorption (limited to alcohol, some medicines, and water) are the three main tasks carried out by the stomach. When food is consumed, the empty stomach's 20–25 mL capacity can grow to 1.5 L. The stomach contracts during a fast, forcing the mucosa and submucosa into discrete folds known as rugae. The cardia, fundus, body (corpus), and pyloric antrum are the anatomical divisions of the stomach. In an open resting condition, the pylorus—the aperture between the stomach and small intestine—is around 12 to 13 mm wide, but larger things can pass through it if the sphincter muscle relaxes more.

While the antrum is the primary location for mixing action and serves as a pump for gastric emptying via thrusting activities, the fundus and stomach body serve as a storage for undigested material. The pylorus, which divides the stomach from the duodenum, is crucial for the stomach's ability to retain food. But from the fasting to the fed state, the pattern of stomach motility is different.

Objectives Of The Study

1. A comparative investigation of drug release in vitro
2. Analysis of the improved formulation's gastroretentive and in vivo pharmacokinetic properties.

REVIEW OF LITERATURE

Bhardwaj et al. Al. (2017) arranged the modified solvent evaporation method for the purpose of classifying and optimizing the pharmacokinetics of novel floating microspheres of metronidazole. They also examined the use of unique systems that are capricious, such as stirring charge, emulsifier awareness, and the development of floating microspheres of metronidazole as a version drug. In a unique ratio, Eudragit S100 and Eudragit RS100 were employed as polymers to create microspheres. It was determined that metronidazole's unusual floating microspheres developed correctly and shown excellent float residences.

Sahu et al. al. (2017) developed and assessed floating-mucoadhesive microspheres of a novel natural polysaccharide for ranitidine hydrochloride shipment to specific websites. Tamarindus indica (TI) seeds were used to extract polysaccharide. A few physicochemical characteristics are assessed for the extracted polysaccharide. With the use of extracted polysaccharides as mucoadhesive excipients and eudragit as a launch-controlling polymer through the emulsion crosslinking process, floating-mucoadhesive microspheres were created. Epichlorohydrin was used to help finish the chemical crosslinking process. With the use of Fourier rework infrared spectroscopy (FT-IR), prepared microspheres were assessed for their drug-polymer compatibility. Additional characterization was completed, including in vitro buoyancy, swelling index, length, surface homes, % encapsulation, and drug launch. The polysaccharide of TI was shown to be suitable for use as an excipient in the production of floating-mucoadhesive microspheres. Kumar and associates.

Al. (2017) developed and assessed a floating drug transport device for curcumin to treat ulcers and stomach cancers. Curcumin, Psyllium husk, HPMC K 15 M, HPMC K 100 M, and Mangiferaindicagum were used in unusual ratios to create floating pills utilizing the moist granulation process. With the help of the granulating agent, a sell-off mass was created once the corresponding powders were thoroughly mixed.

After the dump mass is surpassed by sieve range 10, it is dried for 30 minutes at 50 °C in a warm air oven. To achieve consistency in the granules, they were passed through sieve number 22 after drying. The curcumin floating pill device is a promising floating drug transport machine for oral sustained administration of curcumin. Lastly, optional ingredients such as magnesium stearate and talc have been delivered and finely combined to educate the floating tablet for extended gastric residence time and extended drug bioavailability for the treatment of gastric hassle.

METHODOLOGY AND WORK PLAN

The following materials that were AR/LR grade or extra pure grade available will be used as supplied by the manufacturer without further purification or investigation.

Materials to be Used

The following materials will be used in the research work.

Table-4.1: Materials and their sources

Sl. No	Materials	Source
1.	Losartan potassium	Gift sample from Alkem, (Batch number LP0980610) Taloja.
2.	Alfuzosin Hydrochloride	Gift sample from Wockhardt Research centre, Aurangabad
3.	Hydroxy propyl methyl cellulose K4M and K15M	Gift sample from Colorcon Asia Limited,Goa
4.	Carbopol 934P	SD Fine Chemical, Mumbai
5.	Sodium alginate	Genuine Chemicals, Mumbai
6.	Lactose	SD Fine Chemical, Mumbai
7.	Microcrystalline cellulose	SD Fine Chemical, Mumbai
8.	Poly vinyl pyrrolidone	Genuine Chemicals, Mumbai
9.	Sodium bicarbonate	Qualigens Pharma, Mumbai
10.	Citric acid	SD Fine Chemical, Mumbai
11.	Talc	SD Fine Chemical, Mumbai
12.	Magnesium stearate	Central drug house limited

EQUIPMENTS USED

The following equipments will be used in the present work

Table-4.2: Equipments and their sources

Sl. No.	Equipments	Source
1.	Tablet compression machine	Clit pilot press
2.	UV-Vis spectrophotometer	Pharmaspec UV-1800 Shimadzu
3.	Electronic Balance	Shimadzu BL-220H
4.	Tablet dissolution tester USP XXIII	Electrolab TDT-06N
5.	Hardness tester	Monsanto
6.	Friability test apparatus	Riche-Rich Pharma, Bangalore
7.	Oven	Temp Equipments
8.	IR Spectrophotometer 1615 Series	Perkin-Elmer

Preparation of GRDDS of Losartan potassium and Alfuzosin Hydrochloride

In the present work, wet granulation method has been employed to prepare GRDDS of Losartan potassium and Alfuzosin Hydrchloride with hydroxy propyl methyl cellulose (HPMC) of different viscosity grades, (viscosities 4,000cps, 15,000cps) and other polymers like 224arbopol 934P and sodium alginate, each with different drug to polymer ratios as per the composition given in table no.5&6. Lactose and microcrystalline cellulose were used as diluents along with sodium bicarbonate and citric acid as gas generating agents and PVP (3%w/v solution) as binder, magnesium stearate was used as lubricant and talc as a glidant.

Procedure for preparation of GRDDS of Losartan potassium and Alfuzosin Hydrochloride

All the ingredients were accurately weighed, passed through sieve no. 60 and transferred to a clean porcelain mortar except magnesium stearate and talc. PVP (3% w/v) binding solution is added to the mixture in the mortar in small quantities, thorough mixing of the mixture is done 224arbo a coherent mass is formed. Then it is passed through sieve no.12 and the wet granules were spread on a paper and dried in hot air oven at 30^0C-40^0C for 30 minutes.

RESULTS AND DATA INTERPRETATION

Table 5.1: Composition Of Grhbscapsules Of Hctz

Formulation code	Carbopol974P	SodiumCMC	HPMC K15M	HPMCK4M	Ethylcellulose	Methyl cellulose	EudragitS100	EudragitL100	Drug (HCTZ)	Totalweight (mg)
F IH	150.00	---	---	---	---	---	---	---	50.00	200
F IIH	75.00	---	---	---	75.00	---	---	---	50.00	200
F IIIH	75.00	---	---	---	---	75.00	---	---	50.00	200
F IVH	75.00	75.00	---	---	---	---	---	---	50.00	200
F VH	75.00	---	75.00	---	---	---	---	---	50.00	200
F VIH	50.00	50.00	---	---	50.00	---	---	---	50.00	200

F VIIH	50.00	---	---	50.00	50.00	---	---	---	50.00	200
F VIIIH	50.00	---	50.00	---	---	50.00	---	---	50.00	200
F IXH	50.00	50.00	---	---	---	50.00	---	---	50.00	200
F XH	---	150.00	---	---	---	---	---	---	50.00	200
F XIH	---	75.00	75.00	---	---	---	---	---	50.00	200
F XIIH	---	75.00	---	---	---	75.00	---	---	50.00	200
F XIIIH	---	50.00	50.00	---	---	50.00	---	---	50.00	200
F XIVH	---	75	---	75	---	---	---	---	50.00	200
F XVH	---	---	75.00	---	75.00	---	---	---	50.00	200
F XVIH	---	---	100.00	---	50.00	---	---	---	50.00	200
F XVIIH	---	---	125.00	---	25.00	---	---	---	50.00	200
F XVIIIH	---	---	137.50	---	12.50	---	---	---	50.00	200
F XIXH	---	---	12.50	---	137.50	---	---	---	50.00	200
F XXH	---	---	75.00	---	---	75.00	---	---	50.00	200
F XXIH	---	---	50.00	---	---	50.00	50.00	---	50.00	200
F XXIIH	---	---	75.00	---	---	---	75.00	---	50.00	200
F XXIIIH	---	---	100.00	---	---	---	50.00	---	50.00	200
F XXIVH	---	---	112.50	---	---	---	37.50	---	50.00	200
F XXVH	---	---	75.00	---	---	---	---	75.00	50.00	200
F XXVIH	---	---	50	---	---	50	---	50	50	200
F XXVIIH	---	---	---	75	---	75	---	---	50	200
F XXVIIIH	---	---	---	50	---	50		50	50	200
F XXIXH	---	---	200.00	---	---	---	---	---	50.00	250

F XXXH	---	---	100.00	---	---	---	100.00	---	50.00	250
F XXXIH	---	---	133.33	---	---	---	66.67	---	50.00	250
F XXXIIH	---	---	150.00	---	---	---	50.00	---	50.00	250
F XXXIIIH	---	---	66.67	---	---	---	133.33	---	50.00	250
F XXXIVH	---	---	50.00	---	---	---	150.00	---	50.00	250
F XXXVH	---	---	250.00	---	---	---	---		50.00	300

- **Pre-formulation studies for the selection/ screening of polymers and weight adjustment of the GR HBS capsules of HCTZ**

HCTZ and a number of low-density polymers, including 226arbopol 974P, sodium carboxymethylcellulose (NaCMC), HPMC K4M, HPMC K15M, methylcellulose, ethylcellulose, eudragit S100, and eudragit L100, were tested for buoyancy and matrix integrity in vitro as part of the pre-formulation studies. In order to determine the ideal weight for the formulation development of GR HBS capsules, the capsule fill weight was also adjusted during the trial from 200 to 300 mg.

TABLE5.2:MATRIXINTEGRITYANDFLOATINGBEHAVIOUROFHCTZGRHBSCAPSULESINSGFWITHOUTPEPSIN AT 100 RPM (USING USP TYPE II DISSOLUTION APPARATUS)

Formulation code	Matrix integrity n=6	Floating/ Buoyancytime n=6
FXIIIH	+ + +	+ + +’
FXVIH	+ + +	+ + +
FXVII“	+ + + +	+ ” + +
FXVIIIH	+ + + +	+ + + +
FXXIIH	+ + + +	+ + + +
FXXIIIH	+++++	+++++
FXXIVH	++++	++++
FXXVH	+ + + +	+ + + +
F XXVIIH	+ +	+ +
F XXIXH	+ + + + +	+ + + + +

GR HBS capsules were made with either eudragit S 100 or HPMC K15M by themselves. For 12 hours, only one formulation (XXIIIH) with a fill weight of 200 mg was able to float and maintain matrix integrity. Only HPMC K15M was present in formulations F XXIXH (capsule fill weight = 250 mg), F XXXVH (capsule fill weight = 300 mg), and F XXIIIH (capsule fill weight = 200 mg), whereas F XXXIH (capsule fill weight = 250}) contained HPMC K15M and eudragit S100 in a 3:1 ratio.

- **DissolutionstudyinSGFwithoutpepsin**

USP type II (paddle type) dissolution apparatus was used to conduct in vitro drug release experiments in SGF without pepsin for formulations that demonstrated matrix integrity and floatation time ≥ 12 hours at 100 rpm. The dissolution

medium employed was 900ml of SGF without pepsin, kept at 37±0.5OC. Five milliliters of the sample were stakeat regular intervals of one hour. The sampling process lasted for twelve hours. To keep the sink conditions constant, 5 cc of the dissolving medium was added to the medium each time. Using SGF without pepsin as a blank, the samples were exposed to UV analysis at 271.5 nm (the measured λmax of hydrochlorothiazide in SGF without pepsin).

TABLE5.3:INVITRORELEASEOFHCTZFROMTHEFORMULATIONFXXIIIHINSGFWITHOUT PEPSIN

Time(hours)	Mean absorbance n =6 (±SD)	Concentration (µg/ml)	Amount of drugreleased (mg)	Cumulative% drugreleased
1	0.0856±0.0120	1.0687	2.886	5.77
2	0.1319±0.0095	1.8731	5.057	10.11
3	0.1820±0.0111	2.7431	7.406	14.81
’	0.2484±0.0272	3.8966	10.521	21.04
5	0.“091±0.0055	4.9498	13.365	26”73
6	0.3843±0.0193	6.2544	16.887	33.78
7	0.4327±0.0107	7.0949	19.156	38.31
8	0.5304±0.0149	8.7924	23.74	47.48
9	0.6001±0.0118	10.0019	27.005	54.01
10	0.6589±0.0079	11.0224	29.761	59.52
11	0.6838±0.0138	11.4545	30.927	61.86
12	0.7600±0.0255	12.7778	34.500	69.00

CONCLUSION

Hydrodynamic stress affected the dissolving and mass transfer rate of the drug from the GR HBS capsules (both of HCTZ and propranolol HCl), according to a dissolution research conducted in phosphate citrate buffer pH 3 at paddle rotation rates of 50 and 75 rpm. Propranolol HCl GR HBS formulation F VPL (containing 80mg propranolol HCl; 256mg HPMC K15M; 64mg eudragit S 100 and 48mg lactose) and HCTZ GR HBS formulation "F XXXIHLC" (containing 50mg HCTZ; 133.33mg HPMC K15M, 63.34mg eudragit S100, and 15.83mg lactose) were selected as optimized formulations based on the in vitro performance.

While all GR HBS capsules of propranolol HCl demonstrated non-Fickian (anomalous) release in all dissolution media used, all HPMC-eudragit-based GR HBS capsules of HCTZ demonstrated super case II release in SGF without pepsin and SGF (with the data more fit in zero order model than first and Higuchi model); and non-Fickian anomalous behavior in citrate phosphate buffer pH 3 containing 0.5% SLS.

The medication and polymers did not interact, according to interaction experiments conducted using FTIR and UV spectrophotometry. The optimized HCTZ GR HBS capsule's FTIR and UV spectra showed peaks that like those of the pure HCTZ, and the optimized propranolol HCl GR HBS capsule's FTIR and UV spectra showed peaks that resembled those of the pure propranolol HCl.

In SGF (as the dissolution medium), a comparative dissolution study was conducted between the commercially available prolonged release propranolol HCl capsule (BETACAP TR 80, Sun Pharma Laboratories Ltd., East-Sikkim, India) and the optimized GR HBS capsule. The dissolution profiles of the two formulations were shown to differ by the model-

independent technique that compared the dissolution data using the difference factor (f1) and similarity factor (f2). Additionally, a comparison of the dissolution profiles of the optimized GR HBS capsule of propranolol HCl and the controlled release dosage form of the drug (controlled release coated pellets encapsulated into hard gelatin capsules, "United States Patent US 2003/0185887 A1-2002") using a model independent method showed that the two had similar dissolution profiles.

The dissolution profiles of the optimized GR HBS capsules of HCTZ and the commercial Dichlotride tablet with 50 mg of hydrochlorothiazide (Merck Sharp & Dohme, N. J.; USA) and the self-made immediate release (IR) capsule of HCTZ with 50 mg of HCTZ were compared. In contrast to the marketed Dichlotride tablet, which released 100% of the drug within one and a half hours, and the self-prepared IR capsule, which released 100% of the drug within an hour, the study showed that the drug release from the optimized GR HBS capsules of HCTZ was sustained for 12 hours, indicating greater utility of the optimized GR HBS capsule. Rabbits were used in in vivo experiments to evaluate the pharmacokinetic characteristics and buoyancy of optimized GR HBS formulations.

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