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FORMULATION AND EVALUATION OF FLOATING TABLET OF TELMISARTAN

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Abstract:

The aim of present investigation was to formulate and evaluate floating tablet of telmisartan. Telmisartan is a non-peptide angiotensin II receptor antagonist. Telmisartan blocks the vasoconstriction and aldosterone secreting effects of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland, leading to a reduction in arterial blood pressure. The poor bioavailability of Telmisartan (40-58%) was the criteria which caused the selection of drug, which could be increased by prolonging the gastric retention time so that it remain in the acid environment until all the drug is released. U.V. Scanning of Telmisartan was performed and the λ_{max} at 295 nm was found to be the most appropriate for the determination of concentration of unknown samples. Standard curve of telmisartan was prepared at in 0.1N HCl and the correlation was found to be 0.992 respectively. The tablets of various formulations of telmisartan were prepared and the tablet hardness was found to be in range of 3.01 to 8.24 kg/cm^3. The average weight of the prepared tablets of various formulations was found to be with in the Pharmacopoeial limit i.e. ± 7.5% The average percentage (%) drug content was also found with in the Pharmacopoeial limit and shows the effectiveness of the mixing procedure. Formulation F4, F8, F12 having 12 mg MKG content were showing 72.37±2.78, 69.23±2.72, 68.87±3.89 cumulative drug release in 12 hrs. in case of formulations F1, F1, F5, F9, having katira gum content 9 mg were showing 83.52±2.22, 81.56±2.47, 82.71±2.95. From the results obtained, it was concluded that the formulation F7 is the best formulations as the extent of drug release was found to be around 75.44%. This batch also showed immediate floatation and floatation duration of more than 8hr. The drug release model of this formulations comply with Peppas model kinetics.

KEYWORDS: *Telmisartan, Gond Katira., Avicel-101, 0.1 N HCl , Methanol, Magnesium sterate, Talc*

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INTRODUCTION:

The oral route of administration is considered as the most widely accepted route.But the most evident drawback of the commonly used oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patients incompliance particularly in case of pediatric and geriatric patients. Convenience of administration and patient compliance are gaining significant importance in the design of dosage forms. Recently more stress is laid down on the development of organoleptically elegant and patient friendly drug delivery system for pediatric and geriatric patients. So, a new delivery system known as oral fast dissolving/disintegrating (FDDS)/melt-in mouth tablets gaining importance. These oral dosage forms dissolve rapidly in saliva and can be swallowed without the need of drinking water. Elimination of bitterness is an important criterion in product formulation of mouth dissolving tablets. Super-disintegrants are added in formulation to increase the dissolution characteristics thus increasing bioavailability of drug. There are three methods of addition of disintegrant into the formulation, intra-granular (Internal addition), extra-granular (External addition), partly intra-granular and extra-granular addition. The time for disintegration of orally disintegrating tablets is generally considered to be less than one minute. Although patients can experience actual oral disintegration times that typically range from 5-30 sec. Fast dissolving tablets are prepared by various techniques such as direct compression, solid dispersion and moulding. The simple process and cost effectiveness of direct compression process prefer this process over
Fast dissolving Tablets are disintegrating and/or dissolve rapidly in the saliva without the needfor water (1-3).

The successful development of oral controlled drug delivery systems requires an understanding of the three aspects of the system, namely

1. The physiochemical characteristics of the drug.
2. Anatomy and physiology of GIT and Characteristics of Dosage forms

Good fundamental understanding of the anatomic and physiological characteristics of the human GIT is required to modulate the gastrointestinal transit time of a drug through FDDS for maximal gastrointestinal absorption of drugs and site-specific delivery(4-6). Gastro retentive systems 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 for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients(7). To successfully modulate the gastrointestinal transit time of a drug delivery system through floating drug delivery system (FDDS) For maximal gastrointestinal absorption of drugs and site-specific delivery, one needs to have a good fundamental understanding ofthe anatomic and physiological characteristics of the human GIT. These are outlined and briefly discussed (8). The main function of the stomach is to process and transport food. Itserves as a short-term storage reservoir, allowing a rather largemeal to be consumed quickly. Substantial enzymatic digestion Is initiated in stomach, particularly of proteins. Vigorous contractionsof gastric smooth muscle mix and grind foodstuffs with gastricsecretions, resulting in liquefaction of food. As food is liquefied in the stomach, it is slowly released into the small intestine for further processing(9).Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and bodyacts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastricemptying by propelling actions(10).It has been reported that the mean value of pH in fasted healthy subjects is 1.1± 0.15. But when food comes into the stomach, the pHmay rise to levels in the 3.0 to 4.0 level due to the buffering capacity of proteins. However, in fasted state, basal gastric secretion in women is slightly lower than that of men Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an inter-digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the inter-digestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases:

1. Phase I (Basal phase) lasts from 30 to 60 minutes with rare contractions.
2. Phase II (Preburst phase) lasts for 20 to 40 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
3. Phase III (burst phase) lasts for 10 to 20 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.
4. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles(11).

Factors Affecting Gastric Residence Time of FDDS:

Formulation factors:

a) Size of tablets: Retention of floating dosage forms in stomach depends on the size of tablets. Small tablets are emptied from the stomach during the digestive phase, but large ones are expelled during the house keeping waves [(12)]. Floating and non floating capsules of 3 different sizes having a diameter of 4.8 mm (small units), 7.5 mm (medium units), and 9.9 mm (large units), were formulated and analyzed for their different properties. It was found that floating dosage units remained buoyant regardless of their sizes on the gastric contents throughout their residence in the gastrointestinal tract, while the nonfloating dosage units sank and remained in the lower part of the stomach. Floatingunits away from the gastro-duodenal junction were protected fromthe peristaltic waves during digestive phase while the nonfloatingforms stayed close to the pylorus and were subjected to propelling and retropelling waves of the digestive phase

b) Density of tablets: Density is the main factor affecting the gastric residence time of dosage form. A buoyant dosage form having a density less than that of the gastric fluids floats, since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period. A density of less than 1.0g/ml i.e. less than that of gastric contents has been reported. However, the floating force kinetics of such dosage form has shown that the bulk density of a dosage form is not the most appropriate parameter for describing its buoyancy capabilities [14-15].

c) Shape of tablets: The shape of dosage form is one of the factors that affect its gastric residence time. Six shapes (ring tetrahedron, cloverleaf, string, pellet, and disk) were screened in vivo for their gastric retention potential. The tetrahedron (each leg 2cm long) rings (3.6 cm in diameter) exhibited nearly 100% retention at 24 hr [16].

d) Viscosity grade of polymer: Drug release and floating properties of FDDS are greatly affected by viscosity of polymers and their interaction. Low viscosity polymers (e.g., HPMC K100 LV) were found to be more beneficial than high viscosity polymers (e.g., HPMC K4M) in improving floating properties. In addition, a decrease in the release rate was observed with an increase in polymer viscosity [17].

Idiosyncratic factors:

a) Gender: Women have slower gastric emptying time than do men. Mean ambulatory GRT in meals (3.4±0.4 hours) is less compared with their age and race-matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface [18].

b) Age: Low gastric emptying time is observed in elderly than do in younger subjects. Intra-subject and inter-subject variations also are observed in gastric and intestinal transit time. Elderly people, especially those over 70 years have a significantly longer GRT[19].

c) Posture:

i) Upright position: An upright position protects floating forms against postprandial emptying because the floating form remains above the gastric contents irrespective of its size. Floating dosage forms show prolonged and more reproducible GRTs while the conventional dosage form sink to the lower part of the distal stomach from where they are expelled through the pylorus by antral peristaltic movements[20].

ii) Supine position: This position offers no reliable protection against early and erratic emptying. In supine subjects large dosage forms (both conventional and floating) experience prolonged retention. The gastric retention of floating forms appear to remain buoyant anywhere between the lesser and greater curvature of the stomach. On moving distally,these units may be swept away by the peristaltic movements that propel the gastric contents towards the pylorus, leading to significant reduction in GRT compared with upright subjects [21-22].

d) Concomitant intake of drugs: Drugs such as prokinetic agents (e.g., metoclopramide andcisapride), anti Cholinergics (e.g., atropine or propantheline), opiates (e.g., codeine) may affect the performance of FDDS. The co-administration of GI-motility decreasing drugs can increase gastricemptying time [23].

e) Feeding regimen: Gastric residence time increases in the presence of food, leading to increased drug dissolution of the dosage form at the most favorable site of absorption. A GRT of 4-10 h has been reported after a meal offats and proteins [24].

Suitable Drugs for Gastroretention: Delivery of the Drugs in continuous and controlled manner have a lower level of side effects and provide their effects without the need for repeated dosing or with a low dosage frequency. Sustained release in the stomach is also useful for therapeutic agents that the stomach does not readily absorb, since sustained release prolongs the contact time of the agent in the stomach or in the upper part of the small intestine, from where absorption occurs and contact time is limited [25] Appropriate candidates for controlled release gastroretentive dosage forms are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT.

1. Narrow absorption window in GI tract, e.g., riboflavin and levodopa
2. Basically absorbed from stomach and upper part of GIT, e.g., chlordiazepoxide and cinnarazine.

3. Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate.
4. Locally active in the stomach, e.g., antacids and misoprostol.

MATERIALS AND METHOD:

MATERIALS USED

Table 1: List of materials used in the preparation of formulation

S. No.	Material	Source
1.	Telmisartan	Cipla Mumbai
2.	Katira Gum	Signet Chemicals Pvt.Ltd., Mumbai
3.	Avicel-101	Central Drug House (P) Ltd. India.
4.	Sodium bicarbonate	Sunchem Private Ltd
5.	Magnesium stearate	Central Drug House (P) Ltd. India.
6.	Hydrochloric acid	Central Drug House (P) Ltd. India
7.	Talc	Central Drug House (P) Ltd. India.

METHODS

Preparation of floating tablets:

Direct Compression Method

All the excipients were passed through 60 # sieve and drug (telmisartan) was mixed geometrically with the sieved excipients and blended by tumbling method in a sealable polybag. The powder blend was then compressed directly on single stroke multi punch machine (AK Industries, Nakodar, Punjab, India) using 6 mm flat round shaped die punch tooling. The formula for the preparation of FDTs is as under:

Table 2 : The formula for the preparation of FDTs

Ingredients Mg/tablet	Formulations											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Telmisartan	20	20	20	20	20	20	20	20	20	20	20	20
Avicel 101	72	72	72	72	77	77	77	77	82	82	82	82
Katria Gum (MKG)	9	10	11	12	9	10	11	12	9	10	11	12
Sodium bicarbonate	5	5	5	5	4	4	4	4	3	3	3	3
Magnesium sterate	1	1	1	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1	1	1	1

RESULT AND DISCUSSION:

Preformulation studies

The key component of a preformulation study is to characterize the chemical and physical properties of drug substance. FT-IR, UV-Visible spectrophotometery, melting point, solubility and partition coefficient were used for identification of chemical and physical properties of Telmisartan.

6.1 Scanning for λmax of Telmisartan

UV scan of Telmisartan was done in 0.1 N HCl of pH 1.2 and λ_{max} comes out to be 295 nm. As shown in figure 9 it indicate the purity of drug.

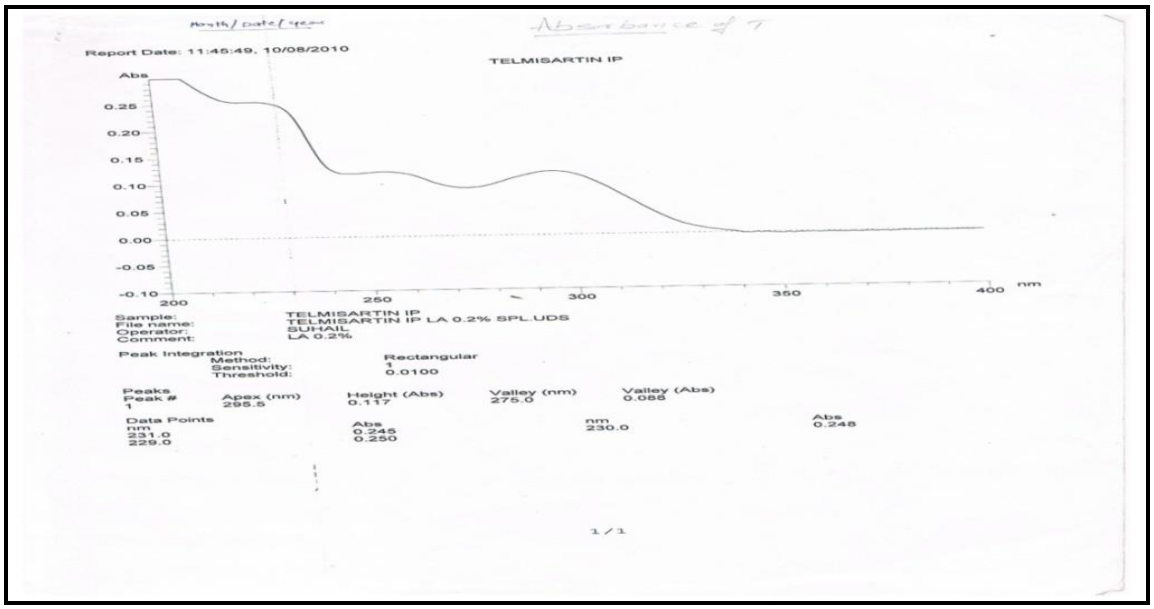

Figure 1: U.V. Scan of Telmisartan in 0.1 N HCl (pH 1.2)

6.1 FT-IR Spectrum

6.1.1 FT-IR Spectrum pure drug

FT-IR (Fourier Transform Infrared) spectrum of any compound or drug gives information about the groups present in that particular compound. FT-IR Spectroscopy [Shimazu Corporation, (Japan)] was used for structure analysis. The potassium bromide (KBr) disc technique was employed. Figure.10 and Table 8 shows the spectrum and interpretation of FT-IR spectrum of Telmisartan, respectively.

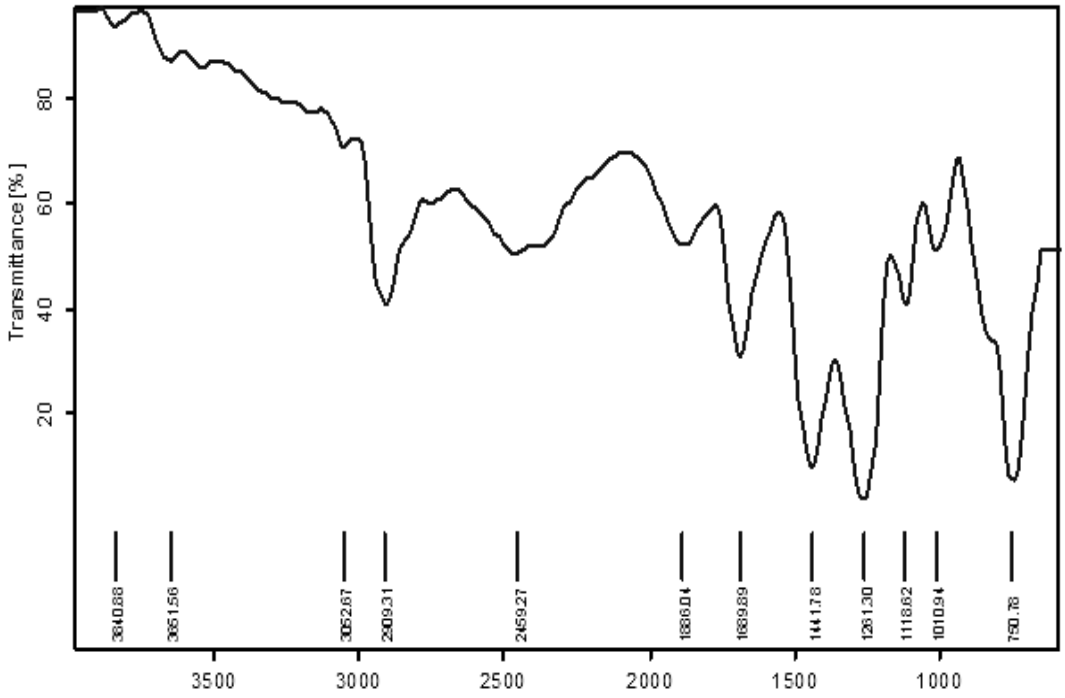

Figure 2: FT-IR spectrum of Telmisartan

Table 3: Interpretation of FTIR spectrum of Telmisartan

Observed Peak(cm^{-1})	Reference Peak(cm^{-1})	Functional group (Vibration)
1689.89	1700-1680	C =O (Stretching)
3052.67	3130-3030	NH (Stretching)
2909.31	2950-2850	C-H (Stretching)
3651.56	3700-3500	OH (Stretching)
1261.30	1280.6	-CN-(gp present)

All these vibration peaks at different wave numbers corresponds to its functional groups, confirming the purity of the drug as per established standards.

FT-IR Spectrum of Katira gum: FT-IR (Fourier Transform Infrared) spectrum of Katira gum was shown in Figure11 and interpretation in Table no: 9 indicate the purity of the gum

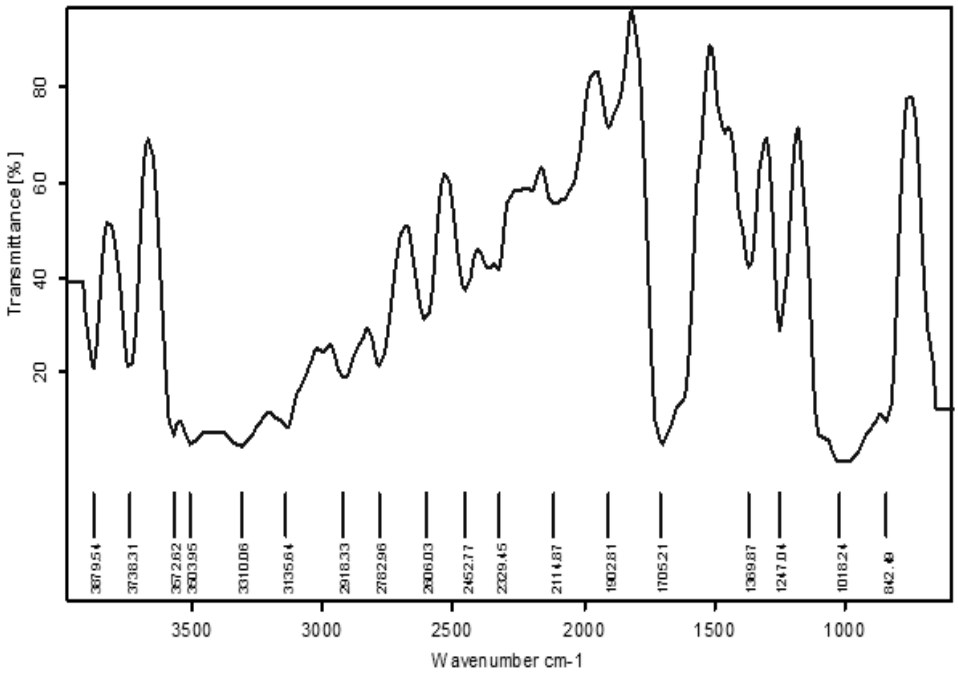

Figure 3: FT-IR Spectrum of Katira gum

Table 4: Interpretation of FT-IR Spectrum of Katira gum

Observed Peak (cm^{1})	Reference peak (cm^{1})	Functional group present
3310.06, 3503.95	3550-3180	O-H
1705.21	1630-1750	C=O
1018.24	1010-1070	C-O
1247.04	1306-1275	C-N

Melting point

The analysis **(Figure 12)** of drug showed a characteristic, sharp endothermic peak at 162 °C corresponding to its melting point which is concordant to reported 162 °C.

Table 5: Melting point of Telmisartan

Drug	Melting point (°C)	
	Observed	**Reported**
Telmisartan	162	161-163

Solubility Study: Solubility of the Telmisartan was determined in various solvents at room temperature. Solubility was found to be 3.487±0.85mg/ml in methanol 0.017 ± 0.005mg/ml in 0.1N HCl, 2.17 ± 0.005 mg/ml in water (Table 11).

Table 6: Solubility profile of Telmisartan in different solvent

Solvents	**Observed(mg/ml)**	**Inference**
Methanol	3.487±0.85	Slightly soluble
0.1 N HCl	2.17 ± 0.005	slightly soluble
Water	0.085 ± 0.0002	Practically insoluble

Partition Coefficient: Partition coefficient of Telmisartan was determined by Shake Flask method and was found to be 3.4±0.12which is closer to the reported value 3.2. The value of partition coefficient reveals that Telmisartan is lipophilic in nature (Table 12).

Table 7: Partition coefficient of Telmisartan

Drugs	**Partition coefficient (log P)**	
	Observed*	**Reported**
Telmisartan	3.4±0.12	3.2

STANDARD CURVE OF TELMISARTAN: Preparation of standard plot by UV method. All the standard plots were prepared in triplicate in the concentration range of (10-60µg/ml).

Table 8: Standard curve of Telmisartan by UV-spectroscopy

Concentration(µg/ml)	**Absorbance**	**Statistical data**
10	0.185	
20	0.355	
30	0.534	y = 1.650 + 0.034
40	0.732	
50	0.881	R^2 = 0.992
60	0.985	

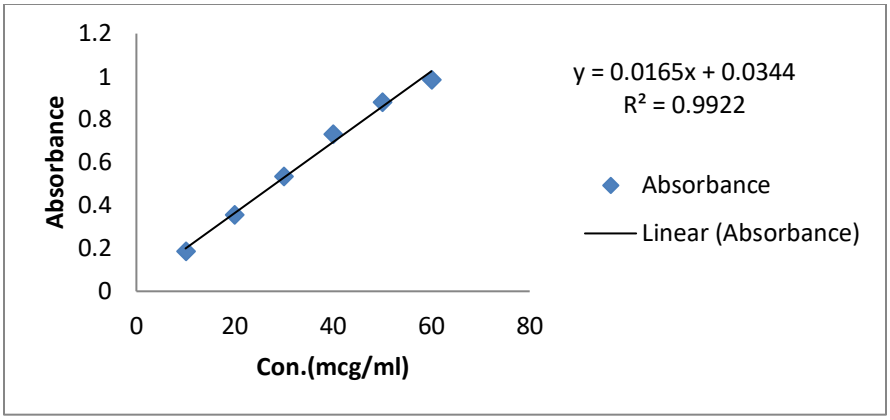

Figure 4: Standard curve of Telmisartan by UV-spectroscopy in 0.1N HCl

Compatibility study: The FTIR spectrum of pure Telmisartan drug and pure polymer (Katira gum) were compared with the spectrum of Physical mixture of drug and polymer. The presences of all characteristic peaks of Telmisartan and Katira gum in the IR spectrum of physical mixture indicated absence of chemical interaction between drug and polymer.

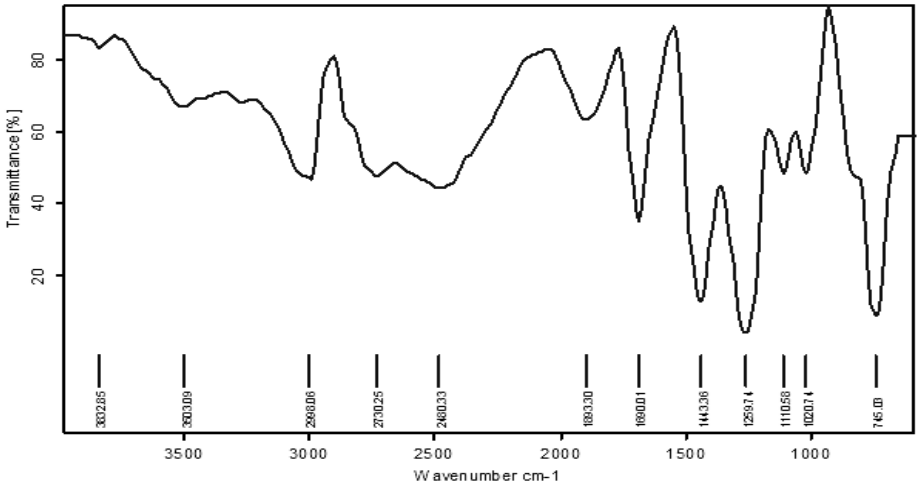

Figure 5: FT-IR spectra of Physical Mixture

Characterization of blends:

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing step and all these can affect the characteristics of blend produced. The characterization of mixed blend was performed for the flow property of powders. Bulk density, tapped density, Hausners ratio, Compressibility index, angle of repose have also been determined.

Bulk Density : Bulk Density of all batches blends was found to be in range of 0.399-0.572 g/cc

Tapped Density : Tapped Density of all batches blends was found to be in range of 0.456-0.575 g/cc

Hausners Ratio Index (%): Hausners Ratio Index of all batches blends was found to be in range of 1.081-1.271 %. Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (> 1.25)

Compressibility Index (%): Compressibility Index of all batches blends was found to be in range of 7.370 -14.231 % that shows good to excellent flow properties because more less than 12 shows excellent flow and 12-16% shows good flow properties

Angle of Repose (ɵ): Angle of repose of all batches blends was found to be in range of 20.261 -24.418. less than 25 shows excellent flow.

Table 9: Characterization of Blends

PARAMETERS					
Parameters / **Formulation**	**Bulk Density (g/cc)**	**Tapped Density (g/cc)**	**Hausners Ratio Index (%)**	**Compressibility Index (%)**	**Angle of Repose(θ)**
F1	0.514 ± 0.001	0.584± 0.003	1.136±0.0007	12.00 ± 0.05	24.418 ± 1.09
F2	0.490 ± 0.002	0.564 ± 0.003	1.150 ± 0.0008	13.079 ± 0.06	23.797 ± 1.21
F3	0.507 ± 0.004	0.575 ± 0.003	1.134 ± 0.0007	11.831 ± 0.05	22.976 ± 0.99
F4	0.498 ± 0.002	0.553 ± 0.002	1.110 ± 0.0005	9.972 ± 0.04	24.132 ± 1.53
F5	0.490 ± 0.003	0.530 ± 0.020	1.081 ± 0.048	10.254± 0.27	23.412 ± 1.17
F6	0.494 ± 0.002	0.548 ± 0.002	1.109 ± 0.0005	9.890 ± 0.04	23.412 ± 1.23
F7	0.352 ± 0.003	0.542±0.0014	1.165±0.0008	7.370±0.03	20.261± 1.23
F8	0.512 ± 0.001	0.456±0.0041	1.123±0.0054	11.321±0.054	24.236± 2.01
F9	0.425 ± 0.002	0.545±0.0021	1.058±0.0041	9.251±0.045	22.541± 1.23
F10	0.399 ±0.003	0.698±0.0052	1.271±0.0024	14.231±0.056	21.354± 1.75
F11	0.478±0.007	0.345±0.0019	1.247±0.0042	13.245±0.075	21.361± 1.32
F12	0.572±0.005	0.456±0.0023	1.087±0.0021	11.32±0.078	21.874± 1.47

Characterization of floating tablets:

1. **General Appearance:** The general appearance of a tablet, its visual identification and over all 'elegance' is essential for cosumer acceptance. This includes tablets size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws, consistency and legibility of any identifying marking
2. **Tablet Thickness:** The thickness of all batches tablet was found to be in range of 2.775-3.125mm(n= 10, the data represents the mean of ten observations).
3. **Tablet Hardness:** The hardness of all batches tablet was found to be in range of 3.01-8.24 Kg/cm^2. Amount of MKG along with Avicel 101 were found to have significant effect on Hardness of the tablets were found to increase from 3.01± 0.0095 -6.2±0.113 (F1-F4), 3.1 ± 0.140-7.26±0.125 (F5-F8), 3.1±0.521-8.24±0.541 (F9-F12), demonstrating the effect of the selected variables on hardness. Hence, both MKG and binder concentration were found to have direct affect on hardness. (n= 10, the data represents the mean of ten observations).
4. **Friability Test:** Another important measure of tablets strength is friability. The values of friability in percentage was found decreased from 1.093 ± 0.042 - 0.595 ± 0.063 (F1-F4), 1.102 ± 0.057-0.721± 0.065 (F5-F8), 1.064±0.045-0.646± 0.098 (F9-F12) The percent friability for those formulations were below 1% indicating that the friability is within the prescribe limits. The results of friability test indicated that the friability value decreases with increase in MKG and binder concentration.
5. **Drug Content:** The percent drug content of drug in all tablet batches was found to be within limits. The percent drug content value of telmisartan was found 81.74±0.034, 98.11±0.04, The results within range indicated uniformity of drug.
6. **Weight Variation Test:** Ten tablets were selected randomly from each batch of katira gum floating tablets and weight individually to check for weight variation as per Indian Pharmacopoeia 2007 were found to be within the specified. In all the formulations the tablet weight was found to be in between of 4.2- 5.2mg, hence 5% maximum difference allowed.

Table 10: Characterization of Floating Tablets

Formulations	Thickness (mm)	Hardness (kg/cm2)	Friability (%)	Drug content (%)	Weight Variation %
F1	2.775 ± 0.014	3.01 ± 0.095	1.093 ± 0.042	92.36 ±0.007	5.1 ± 0.004
F2	2.942 ± 0.026	4.06 ± 0.113	0.901 ± 0.049	93.54±0.013	5.2 ± 0.007
F3	3.043 ± 0.034	5.1 ± 0.159	0.788 ± 0.046	94.86±0.047	4.9 ± 0.002
F4	3.125 ± 0.004	6.2 ± 0.113	0.595 ± 0.063	95.56±0.074	5.2 ± 0.007
F5	2.894 ± 0.037	3.1 ± 0.140	1.102 ± 0.057	91.78±0.042	4.3 ± 0.008
F6	2.812 ± 0.029	4.16 ± 0.127	0.985 ± 0.059	81.74±0.034	5.01 ± 0.008
F7	3.071± 0.041	5.6±0.111	0.654± 0.045	98.11±0.047	4.703± 0.003
F8	3.112± 0.021	7.26±0.125	0.721± 0.065	94.021±0.032	4.87±0.004
F9	2.781±0.009	3.1±0.521	1.064± 0.045	90.75±0.074	4.36±0.005
F10	3.011±0.051	4.18±0.452	0.942± 0.075	87.11±0.045	4.21±0.006
F11	3.102±0.042	6.23±0.36	0.712± 0.063	94.54±0.078	5.06±0.004
F12	3.094±0.036	8.24±0.541	0.646± 0.098	96.75±0.045	4.85±0.0409

***In Vitro* Buoyancy Studies**

All the tablets were prepared by effervescent approach. Sodium bicarbonate was added as a gas-generating agent. Sodium bicarbonate induced carbon dioxide generation in presence of dissolution medium (0.1 M hydrochloric acid). The combination of sodium bicarbonate and Avicel 101 provided desired floating ability and therefore this combination was selected for the formulation of the floating tablets. It was observed that the gas generated is trapped and protected within the gel, formed by hydration of polymer (MKG), thus decreasing the density of the tablet below 1 and tablet becomes buoyant. The tablet swelled radially and axially during in vitro buoyancy studies. In this study, penetration of water into tablets prepared with 11mg MKG was rather slow, causing delayed gel formation and subsequent increase in the floating lag time compared to the tablets prepared with other concentration of MKG.

Table 11: in vitro buoyancy studies of Telmisartan Floating Tablets

Sr. No.	Formulation	Floating lag time (Seconds)	Total floating time (h)
1.	F1	26.4±0.123	12
2.	F2	38.3±0.231	12
3.	F3	47.8±0.145	12
4.	F4	68.3±0.312	12
5.	F5	71.2±0.452	12
6.	F6	115±1.541	12
7.	F7	162.3±1.961	12
8.	F8	90.4±2.147	12
9.	F9	127.3±2.45	12
10.	F10	147.4±2.36	12
11.	F11	137.56±1.75	12
12.	F12	123.5±2.631	12

***In Vitro* Dissolution Studies**

In vitro dissolution studies of the prepared floating tablets of Telmisartan was carried out on USP-II dissolution apparatus using paddle. The dissolution study of all the prepared tablets was carried under following conditions :-

Medium: 900 ml 0.1 N HCl (pH 1.2), RPM: 50 rpm, Sample taken 5 ml, λmax 295 nm

Absorbance for the sample withdrawn were recorded and percent (%) drug release at different time intervals are shown in Table 18 The rate and extent of drug release from the formulated tablet batches was found to be affected by the different concentration of MKG and Avicel 101. The increase in polymer contents was found to reduce the drug release from floating tablets. Formulation F4, F8, F12 having 12 mg MKG content were showing 72.37±2.78, 69.23±2.72, 68.87±3.89 cumulative drug release in 12 hrs. in case of formulations F1, F1, F5, F9, having MKG content 9 mg were showing 83.52±2.22, 81.56±2.47, 82.71±2.95. The reduction in drug release with increase in MKG concentration may

be attributed to decrease in total porosity of the matrices and increase in tortuosity and drug diffusion path length of polymeric matrices

Table 12 In-vitro cumulative percent release of different floating tablets

Time (hr)	Cumulative percent release ± SD											
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
1	2.21±0.98	2±1.15	1.87 ±0.94	2.01±0.81	1.521± 0.51	2.41±0.94	2.22± 1.041	1.85± 1.23	2.51± 1.22	2.31± 0.95	1.87± 0.76	2.74± 0.57
2	6.7±1.32	6.98±2.34	4.21 ±1.34	5.31 ±1.34	4.31 ±1.94	7.31 ±1.24	5.21 ±1.23	6.84 ±2.56	7.85 ±1.25	6.85 ±1.54	4.54± 1.08	6.74 ±1.38
3	15.63 ±2.42	15.06± 1.82	11.01 ±2.84	9.51±2.74	8.57±2.54	11.54± 2.14	10.67 ±1.76	11.32 ±2.81	12.44 ±3.71	9.87± 2.56	10.78 ±2.47	10.85 ±2.54
4	24.41 ±0.95	23.31± 1.44	19.1 ±2.12	16.14±2.12	14.17± 2.21	18.16± 2.72	17.83 ±3.52	20.36 ±3.01	17.42 ±2.52	18.74 ±3.14	18.36 ±1.97	15.74 ±2.11
5	32.41±1.28	33.11± 1.26	27.3± 2.43	24.3± 2.33	21.3± 2.73	26.3± 2.33	27.3± 2.52	25.56 ± 2.34	27.24 ± 2.19	26.41 ± 2.45	23.85 ± 3.12	26.57 ± 2.87
6	45.275±1.46	43.56± 2.22	35.1 ±3.33	29.4 ±3.33	30.4 ±2.83	33 .4 ±3.33	33.74 ±2.87	34.78 ±2.96	38.45 ±5.74	32.78 ±2.98	31.45 ±1.96	32.87 ±2.78
8	61.482±1.32	68±1.72	49.30 ±1.98	44.5±1.98	43.5±1.78	44.5±1.98	46.23 ±2.64	48.54 ±2.74	49.36 ±1.97	47.52 ±2.74	50.87 ±2.74	47.89 ±2.74
10	72.32±2.54	69.56± 3.41	73.45 +3.01	58.74 ±4.58	65.74 ±4.58	58.74 ±4.58	64.85 ±4.64	67.52 ±3.56	61.67 ±5.96	68.54 ±3.74	62.54 ±5.74	59.78 ±2.97
10	72.32±2.54	69.56 ±3.41	73.45+ 3.01	58.74 ±4.58	65.74 ±4.58	58.74 ±4.58	64.85 ±4.64	67.52 ±3.56	61.67 ±5.96	68.54 ±3.74	62.54 ±5.74	59.78 ±2.97
12	83.52 ±2.22	80.12 ±2.62	79.54± 3.12	72.37±2.78	81.56 ±2.47	76.32± 3.12	75.44 ±3.56	69.23 ±2.72	82.71 ±2.95	78.89 ±3.12	71.85 ±5.16	68.87 ±3.89

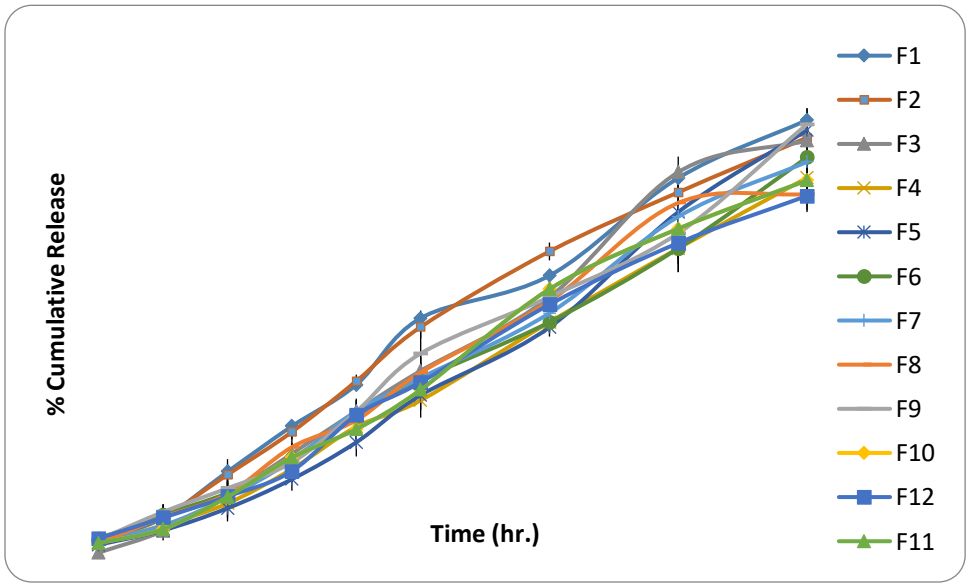

Figure 6: In vitro drug release study of various formulations

Kinetics of drug release

To study the mechanism of the drug release from tablets, the release data were fitted to zero-order, first order, Higuchi equation, and Koresmeyer-pappas equation. The equations for these models are as follows:

a) Zero order equation:

$$Q = k0t$$

Where, Q is the amount of drug released at time t, and k_0 is the release rate constant.

b) First order equation:

\

$$\ln (100-Q) = \ln 100 - k_1 t$$

Where, Q is the amount of drug released at time t, and k_1 is the release rate constant.

c) Higuchi's equation:

$$Q = k_2 t_{1/2}$$

Where, Q is the amount of drug released at time t, k_2 is the diffusion rate constant.

d) Korsmeyer-Peppas equation:

This is often used to describe the drug release behavior from polymeric systems:

$$\text{Log } (Mt/M\infty) = \log k + n \log t$$

Where, Mt is the amount of drug released at time t, M∞ is the amount of drug release after infinite time, and 'k' is a release rate constant incorporating structural and geometric characteristics of the tablet and 'n' is the diffusional exponent indicative of the mechanism of drug release. To clarify the release exponent (n) for different batches of tablet, the log value of percentage drug dissolved was plotted against log time for each batch according to the Korsmeyer equation. A value of n = 0.45 indicates Fickian (case I) release; > 0.45 but < 0.89 for non-Fickian (anomalous) release; and >0.89 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled drug release. The value of 'n' defining Fickian diffusion changes with geometry from 0.5, 0.45 to 0.43 for a slab, a cylinder and a sphere. **(Table-19)** shows the comparative study of different drug release kinetics models & best fit mode & **(Figure-16-19)** shows all the release kinetics of optimized formulation.

Table 13 An overview of the comparative study of different drug release kinetics models & best fit mode. * Regression coefficient (R^2)

Batch	Zero Order Release	First Order Release	Higuchi's Release	Korsmeyer-Peppas Release		Best Fit Model
	R^2	R^2	R^2	Slope (n)	R^2	
F7	0.994	0.851	0.953	0.778	0.996	Korsmeyer-Peppas

*** Regression coefficient (R^2)**

Release kinetics of formulation F7

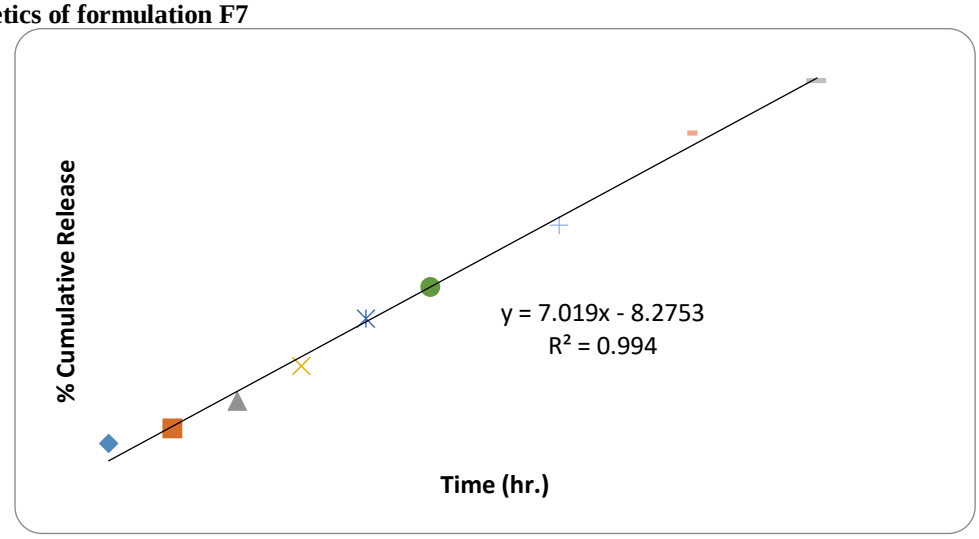

Figure 7. Zero order release kinetics of Formulation F7

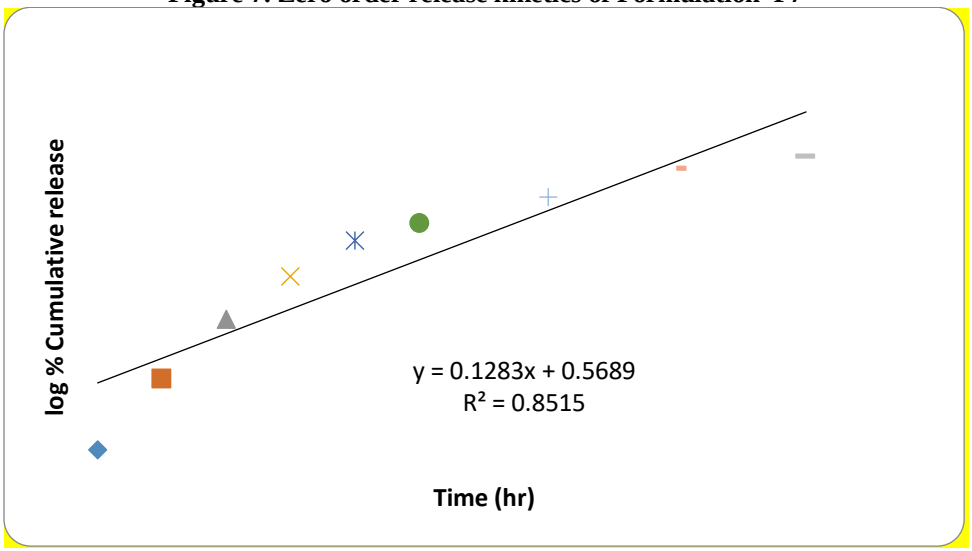

Figure 8. First order release kinetics of Formulation F7

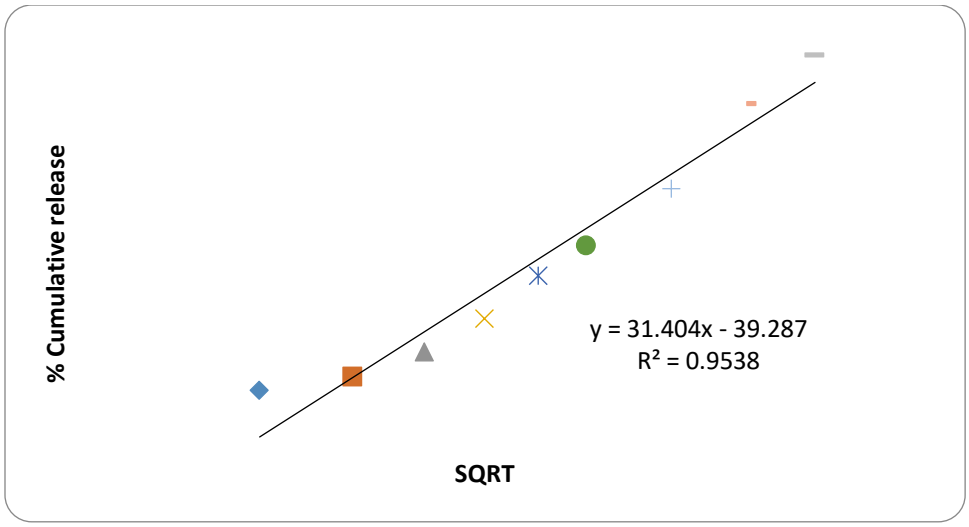

Figure 9. Higuchi model release kinetics of Formulation F7

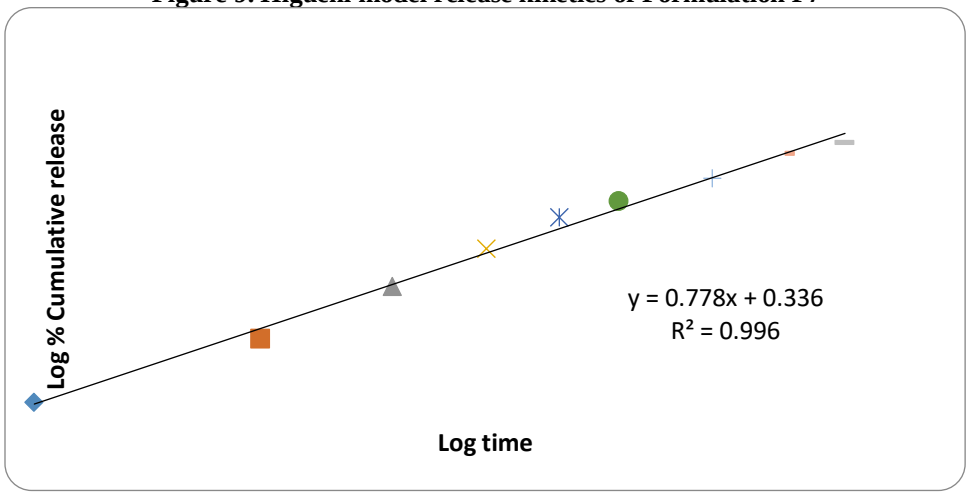

Figure 10. Korsmeyer-Peppas model release kinetics of Formulation F7

Modelling of Dissolution Profiles

The data obtained from dissolution studies of different batches was analyzed using different mathematical model for the determination of release kinetics. The kinetic models used were zero order, first order, matrix model, Hixson-crowell model and Korsmeyer- Peppas model. Most of the batches followed peppas model although some batches also followed zero and higuchi model. It revealed that release mechanism is not well known or more than one type of release phenomenon be involved.

Table 14 Modelling of Dissolution data of formulation F7

Formulation	Zero order		1st order		Higuchi model		Korsmeyer-Peppas	
	R	K	R	K	R	K	R	K
F7	0.994	-8.275	0.851	-0.568	0.953	-39.28	0.9959	14.3648

Determination of Korsmeyer - Peppas Constant

The results of the calculated number n (release exponent) and k (structural and geometric characteristics) of the drug release mechanisms based on in vitro drug release experiments. (N = 3)

n= release exponent, k= structural and geometric characteristics of dosage form.

Table 15. Korsmeyer-Peppas Constants of formulation F7

S. No.	Formulation F7		
		n	**K**
1.	F7	0.778	0.336

Determination of n Value of Korsmeyer-Peppas Equation

To explore the kinetic behavior, results of the in vitro release corresponding to the fraction released equal to or more than 0.6 and less than or equal to 1.0 was fitted to Korsmeyer-Peppas equation in search for the value

of the diffusional exponent n that characterizes the drug transit mechanism (Tables 21). F7 formulation Most showed the value of n between 0.778 indicating anomalus transport mechanism or mass transfer follow a non-fickian transport.

SUMMARY AND CONCLUSION:

Recent scientific and patent literature shows increased interest in academics & industrial research groups regarding novel dosage forms that can be retained in the stomach for prolonged & predictable period of time and the most feasible approach for this is to control the gastric residence time using gastroretentive dosage forms which will provide new & important therapeutic option But the problem can arise if there is a narrow window for drug absorption in the GIT or drug is unstable in the intestinal fluid. So the development of oral controlled dosage form is not just to prolong the drug release but also to ensure the presence of dosage form in the stomach or upper GIT so that drug is released and absorbed for the desired period of time Controlling the residence of a drug delivery system in a particular region of the gastrointestinal tract, can utilize several approaches: intragastric floating systems, high density systems, mucoadhesive systems, magnetic systems, unfoldable, extended or expandable systems and superporous, biodegradable hydrogel systems. Telmisartan is a non-peptide angiotensin II receptor antagonist. Telmisartan blocks the vasoconstriction and aldosterone secreting effects of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland, leading to a reduction in arterial blood pressure. The poor bioavailability of Telmisartan (40-58%) was the criteria which caused the selection of drug, which could be increased by prolonging the gastric retention time so that it remain in the acid environment until all the drug is released. U.V. Scanning of Telmisartan was performed and the λ_{max} at 295 nm was found to be the most appropriate for the determination of concentration of unknown samples. Standard curve of telmisartan was prepared at in 0.1N HCl and the correlation was found to be 0.992 respectively. The tablets of various formulations of telmisartan were prepared and the tablet hardness was found to be in range of 3.01 to 8.24 kg/cm^3. The average weight of the prepared tablets of various formulations was found to be with in the Pharmacopoeial limit i.e. ± 7.5% The average percentage (%) drug content was also found with in the Pharmacopoeial limit and shows the effectiveness of the mixing procedure. From in vitro drug dissolution studies of the different batches of telmisartan, it was observed that The rate and extent of drug release from the formulated tablet batches was found to be affected by the different concentration of MKG and Avicel-101. The increase in polymer contents was found to reduce the drug release from floating tablets. Formulation F4, F8, F12 having 12 mg MKG content were showing 72.37±2.78, 69.23±2.72, 68.87±3.89 cumulative drug release in 12 hrs. in case of formulations F1, F1, F5, F9, having katira gum content 9 mg were showing 83.52±2.22, 81.56±2.47, 82.71±2.95. The reduction in drug release with increase in MKG concentration may be attributed to decrease in total porosity of the matrices and increase in tortuosity and drug diffusion path length of polymeric matrices. From the *in vitro* buoyancy studies, it was found that almost all the batches containing effervescent agent showed immediate floatation followed by specific floatation period. The presence of effervescent agent is must for the floatation of the prepared matrix tablets. From the drug release kinetics modeling, it was analyzed that most of the batches follow Peppas model which indicating more than one type of phenomenon occur in drug release. The values of diffusion exponent 'n = 0.5-1'determined from the Korsmeyer-Peppas equations obtained from modeling of dissolution profiles showing percent drug release of a 60.0% indicates an anomalus transport mechanism and that the mass transfer follows a nonfickian model. From the results

obtained, it was concluded that the formulation F7 is the best formulations as the extent of drug release was found to be around 75.44%. This batch also showed immediate floatation and floatation duration of more than 8hr. The drug release model of this formulations comply with Peppas model kinetics.

CONCLUSION:

The following conclusions can be drawn form the results obtained in this study:

1. A good reproducibility of the physical tests was found for the different batches of system formulation.
2. Viscosity is a major factor affecting the release properties of Gastroretentive Drug Delivery Systems. The higher viscosity seems to inhibit the initial burst effect of telmisartan from the Gastroretentive Drug Delivery Systems.
3. Optimized formulation follow Peppas model indicating more than one type of release phenomenon.
4. The new oral controlled release system shows good in vitro buoyancy in an acidic medium.
5. Presence of effervescent agent (sod. bicarbonate) in the tablets is necessary for in vitro buoyancy.
6. Combinations of MKG and Avicel-101 and/or Avicel-101 blends are good polymer systems for the formulation of floating matrix system.

Based on these conclusions we can certainly say that floating type gastroretentive drug delivery system holds a lot of potential for drug having stability problem in alkaline pH or which mainly absorb in acidic pH. We can certainly explore this drug delivery which may lead to improved bioavailability and ensured therapy with many existing drugs. It is the responsibility of future scientists working in this area to effectively use the potential of this drug delivery system for the benefit of mankind.

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