Review Article

Formulation and Evaluation of Gastro Retentive Drug Delivery System of Tizanidine Hydrochloride: A Review

***Avaru Geetha Dutt, Ande Pratyusha, Uma Maheshwar Rao, Motor Leela Keerthi, Kalakuntla Sai Krishna, Ashok Morsu**

Department of Pharmaceutics, CMR College of Pharmacy, Medchal, Hyderabad, India.

ABSTRACT

Gastro Retentive Sustained Drug Delivery System is a useful approach to avoid impredictable Gastric Empting Time (GET). The incorporation of drug in sustained release Gastro Retentive Dosage forms remains in the stomach for prolonged period of time. Thus, improves the gastric residence time which ultimately increases bioavailability of the drug. Several approaches are used for prolongation of gastric residence time which includes floating drug delivery systems, swelling and expanding systems, bioadhesive systems, modified shape systems, single and multiple unit gas generating systems, high density systems etc. The present interest is to develop floating matrix tablets of Tizanidine HCl (imidazoline derivative) by using Effervescent gas generating systems by incorporating Sodium bicarbonate as gas generating agent. The effect of Citric acid is determined on drug release profile and floating properties. Various viscosity grade polymers like HPMC (K4m&K400m) and Psyllium Husk are used which plays a major role in controlling invitro drug release of the formulation. Different formulations are prepared with different compositions using wet granulation method and evaluated for various physico chemical properties like hardness, thickness, friability drug content, weight variation, floating lag time and floating time of the drug. Based on the invitro drug release, final optimised formula is selected which releases 75% of the drug in 12 hours and remains floating in the gastric fluid for extended period of time. Thus, reduces frequency of dosing.

Keywords: Effervescent system, gas generating system, gastro retentive drug delivery system, sustained drug release, tizanidine hydrochloride

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***Address for correspondence:**
Avaru Geetha Dutt,
Department of Pharmaceutics, CMR College of Pharmacy, Medchal, Hyderabad, India.
E-mail: a.geethadutt@gmail.com

INTRODUCTION [1,2]:

Oral drug delivery system is the most preferable route of drug delivery because of their compact nature, better patient compliance, ease of administration, low cost, flexibility in formulation, and also easy to manufacture, pack and transport.

However, there are some drawbacks associated with oral drug delivery system like short residence time, unpredictable gastric emptying and some times drug may degrade due to the high reactive nature of GI contents. Because of this reason, drugs get absorbed easily from the GI Tract and are disintegrated quickly from the systemic circulation and shows short half life. So, to achieve the desired therapeutic activity usually frequent dosing is required [1].

Oral sustained controlled release formulations are developed to avoid the above limitations, as it releases the drug slowly into GI tract and remains in systemic circulation for extended period of time. Thus, it improves solubility and bioavailability of the drug.

Floating drug delivery system is the most effective and practical approach to increase gastric retention time. Non-effervescent and effervescent systems have been used to develop the floating drug delivery systems, depending upon the mechanism of buoyancy. As a result, it remains floating in the stomach for prolonged period of time without effecting gastric emptying rate [2,3].

Gastric emptying and motility [4]:

It occurs during fed state as well as fasting state. In fed state, the motor activity is induced after digestion of a meal and shows

frequent contractions. In fasting state, inter digestive series of electrical events are characterised in both (inter digestive mylo electric cycle) stomach and small intestine for every 2-3 hours and further divided into 4 consecutive phases.

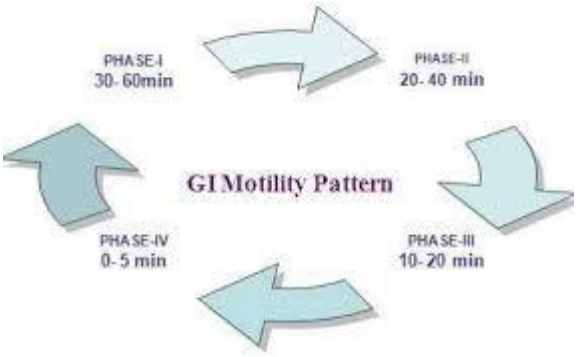

Figure 1: Pictorial Representation of Typical Motility Pattern in Fasting State

Phase-1: It is the basal phase lasting from 40-60minutes with rare contractions.
Phase-2: It is the pre-burst phase lasting from 40-60 minutes and shows contractions due to intermittent action potential.
Phase-3: It is the burst phase lasting from 4-6 minutes and shows large contractions. Therefore, It helps to sweep undigested material out of the stomach. Hence, it is also called as housekeeping wave.
Phase-4: It is the transition phase, which occurs between phase-3 and phase-1 of two consecutive cycles [4].

Table 1: The transit time of different dosage forms across the segment of G. I tract

Dosage Form	Transit Time (h)		
	Gastric	Small intestine	Total
Tablets	2.7-1.5	3.1-0.4	5.8
Capsules	0.8-1.2	3.2-0.8	4.0
Pellets	1.2-1.3	3.4-1.0	4.6
Oral Solution	0.3 -0.07	4.1-0.5	4.4

Objectives:
Gastro retentive floating matrix tablet of Tizanidine HCl is formulated inorder:

- ✓ To study the effect of various factors like drug sodium bicarbonate ratio, drug polymer ratio, duration of floating and release rate pattern.
- ✓ To evaluate the prepared Tizanidine HCl for various properties like hardness, drug content, friability, weight variation etc.
- ✓ To study the release rate pattern of prepared formulations to determine the mechanism of drug release.

Rational for study:
The drugs which are easily absorbed from the GI tract have short half life and are eliminated quickly from the blood circulation, require frequency of dosing. To overcome this problem, controlled release formulations are developed for prolongation of gastric residence time. The present goal of the investigation is to formulate and evaluate gastro retentive floating tablets of Tizanidine HCl which releases the drug in the upper GIT region over an extended period of time and keeps the drug in the region of absorption window. Thus, shows slow release rate of drug and improves bioavailability.
Drug profile [5,6]:
The drug selected for present investigation is Tizanidine HCl, which is a muscle relaxant used in muscle pain and management of spasticity. It acts as an agonist on centrally acting α2 adrenergic receptors, as it is an imidazoline derivative. It also acts as an prokinetic agent which restores motility throughout the GI tract [5]. Tizanidine HCl is very well absorbed from the stomach and less absorbed from the lower intestinal tract, so it is selected as a floating drug delivery system. But it has low bioavailability of 30-40% and posess short

biological half life of 4.2 hours, as it undergoes first pass metabolism. Thus, Tizanidine HCl is the best candidate for floating drug delivery development [6].

Advantages [7-10]:

Gastro retentive drug delivery system is found to be very efficient with the drugs that get absorbed from the intestine.

- ✓ It is used for the treatment of peptic ulcer and meant for local action in the stomach.
- ✓ It increases gastric residence time, thus it improves drug absorption.
- ✓ It minimizes the degradation of drug in the colon and retains the drug in the stomach.
- ✓ As the drug releases slowly at controlled rate, it minimizes the mucosal irritation in the stomach.
- ✓ It reduces the frequency of dosing due to sustained drug delivery.
- ✓ It shows better patient compliance and ease of administration.
- ✓ Fluctuations in drug concentration and adverse effects associated with peak concentration can be reduced.
- ✓ Selectivity in receptor activity is improved to activate different types of receptors.
- ✓ Drug delivery with narrow absorption window in small intestine will show advantages in gastric retention.
- ✓ Counter activity of the body will be reduced with higher drug efficiency.
- ✓ Site specific drug delivery also helps to reduce the dosing frequency.

Disadvantages [11-13]:

- ✓This type of drug delivery requires high fluid content in the stomach for floating action.
- ✓Drugs which undergo first pass metabolism are not suitable for floating systems.
- ✓Sometimes gastric P^H, gastric motility and presence of food in stomach influences gastric retention, which also effects buoyancy.
- ✓The drugs with low stability and low solubility in GI tract are not feasible for floating systems.
- ✓Floating drug delivery system is not suitable for the drugs which cause irritation and lesions to gastric mucosa.

Suitable drug candidates for FDDS [13-18]:

Drugs for FDDS must have better absorption property at upper GI tract and poor colonic absorption.

- ✓Drugs with primary absorption from upper GI tract and stomach.
  (eg- chlordiazepoxide, cinnarazine).
- ✓Drugs with narrow absorption window in GI tract.
  eg - L-dopa, p-ammino benzoic acid, furosemide, riboflavin)
- ✓Drugs with local action in the stomach.
  (eg - microprostol,antacids)
- ✓Drugs with high P^H values and low solubility.
  (eg - diazepam, chlorodiazepoxide, verapamil)

Factors affecting floating drug delivery system [19-22].

Various factors which controls gastric retentive time are as follows:

- ✓Density: Buoyancy of the drug depends upon the density of the dosage form. It must be less than (1.004gm/ml), and remain floating in the stomach for extended period of time without affecting gastric emptying time.
- ✓Size: If the size of the dosage form is greater, gastric residence time will be increased. The diameter of the dosage form with >7.5mm shows greater gastric residence time.
- ✓Shape: Tetrahedron shape of the dosage form with 48 and 22 kilo pounds per square inch shows better gastric retention of 90-100% for about 24hours.
- ✓Nature of meal: Motility pattern of the stomach usually gets changed in the presence of indigested polymers of fatty acids. Thus, gastric emptying time gets decreased and as a result drug release will be prolonged.
- ✓Fed or Unfed state:

- During fasting state, motor activity or migrating myloelectric complex characterizes gastric motility for every 1.5-2hours.
- During fed state gastric motility is longer due to the delay of myloelectric complex.

- ✓Calorie content: A meal with high protein and fat content, increases gastric retention time between 4-10 hours.
- ✓Gender: Mean ambulatory GRT in females is shorter (4.6 ±1.2 hours) when compared to males (3.4 ±0.6hours).

✓Age: People with age 70 and above shows longer GRT.
✓ Disease state: Drug delivery may get effected due to diabetes and crohn's disease.
✓Concomitant drug administration: Floating time of the drug can be affected by opiates like codein and anticholinergics like propantheline and atropine.

Approaches for Gastro-retentive drug delivery system [23-43]:

Retention of an oral dosage form in the stomach has been increased by various approaches.

- High density approach: The density of the pellets should be higher than the stomach fluid of at least 1.50gm/ml, e.g. (coated pellets). Here the drug is mixed with titanium dioxide and barium sulphate [23-26].
- Low density approach: The density of the pellets should be less than 1gm/ml. The pellets release the drug slowly into the gastric fluid for prolonged period of time and remain floating. It is also called Hydro dynamically balanced system [26].

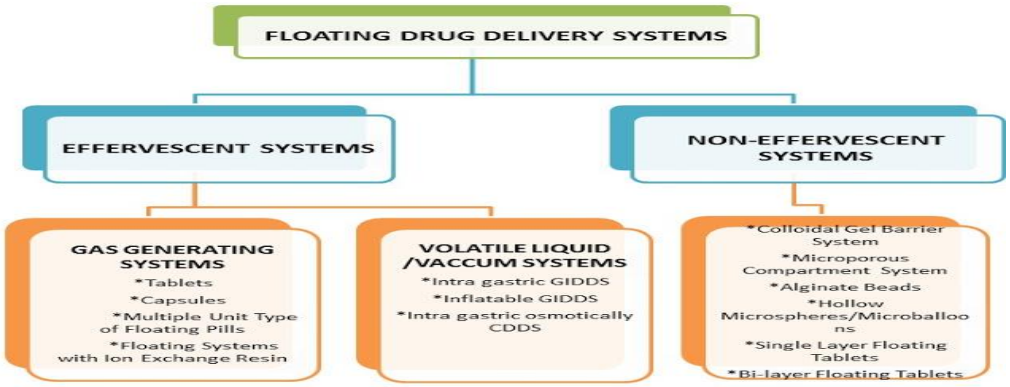

Figure 2: Approaches for Gastroretentive Drug Delivery System

1.Floating systems [27]:
a) Non effervescent FDDS:
-Single layer floating tablets
-Bi layer floating tablets
-Alginate beads
-Hallow microspheres
b) Effervescent FDDS:
i. Gas generating system
-Single unit dosage form
-Multiple unit dosage form
-Floating capsules
ii. Volatile liquid/ vaccum containing system.
2. Swelling and expanding systems
3. Bio adhesive systems
4. Magnetic systems

1. Floating systems:- The bulk density of the system should be less than the gastric fluid, so it remains in floating state for prolonged time periods without affecting gastric emptying rate.

a) Non effervescent FDDS: (Hydro-dynamically balanced system)

In this system, the drug is mixed with gel forming hydrocolloids. After oral administration, it swells in gastric fluid and maintains relative integrity and shape. The hydrocolloid forms a viscous barrier where inner polymers slowly gets hydrated to the surface and facilitates drug release [28].

Polymers like HPMC, HPC, HEC, SCMC, agar and alginic acid are generally used.

- Single layer floating tablets:

The drug mixed with low density enteric materials (such as HPMC, CAP) swells after getting in contact with gastric fluid and maintains bulk density.

- Bi layer floating tablets:

It contains two or more layers, one is immediate release layer, which releases initial dose from the system, while the other layer shows sustained release, which absorbs gastric fluid and forms a colloidal barrier on its surface and also remains in floating state [29].

- Alginate beads:
Freeze dried calcium alginate spherical beads with 2.5mm diameter are prepared by dropping sodium alginate solution into calcium chloride aqueous solution, which causes precipitation of calcium alginate [30-31].

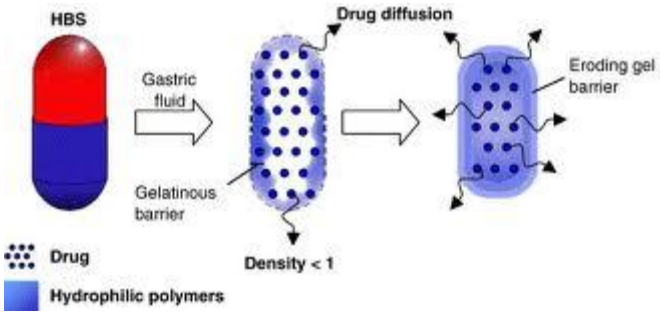

Figure 3: Working Principle of Hydrodynamically Balanced Tablet

- Hollow microspheres:
It is prepared by emulsion solvent diffusion method, by loading the drug (ethanol dichloromethane solution) in an outer enteric acrylic polymer which is poured into PVA aqueous solution.
Polymers generate gas and evaporates dichloromethane, such that, microsphere floats continuously over the acidic media for 12hours [32-33].
b) Effervescent FDDS [34-36]:
These floating systems include swellable polymers like methocel, polysaccharides, which in contact with stomach releases carbon dioxide gas and facilitate floating in the stomach.
i) Gas generating systems:
Gas generating agents such as carbonates and organic acids produce carbon dioxide gas in contact with gastric fluid.
- Single unit dosage form:
The fluid filled system contains fluid filling floating chamber type of dosage form, incorporated into micro porous component which acts as a drug reservoir. It contains 2 apertures, through which GI fluid enters into it to dissolve the drug and the shell gets disintegrates after complete release of the drug.
- Multiple unit dosage form:
It has high loading capacity, with internal hallow structure and should have excellent floatability in carbon dioxide. The diameter of the dosage form must be 8-12mm in their expanded state.

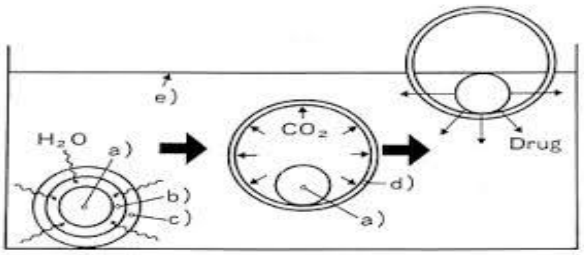

Figure 4: Mechanism of Gas Generating System

-Floating capsules:
A mixture of sodium alginate and sodium bicarbonate is filled in floating capsule, which when comes in contact with acidic fluid liberates carbon dioxide gas and floats on the system. [37].
ii) Volatile liquid/vaccum containing systems:
The inflantable chamber is incorporated into the system containing liquid ether which liberates carbon dioxide gas at body temperature. This chamber inflates automatically and retains drug reservoir compartment within the stomach and releases the drug from the reservoir [38].

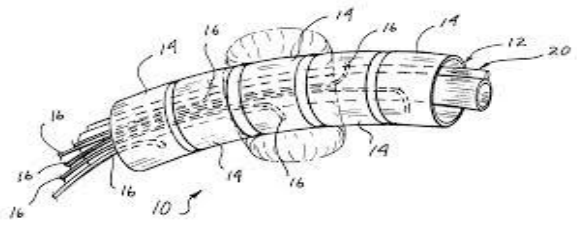

Figure 5: Inflatable Gastrointestinal Delivery System

2. Swelling and expandable systems:
Highly swellable cellulose type hydrocolloids and matrix forming polymers like HPMC, polymethacrylate, polyacrylate, sodium alginate etc are used to swell the polymer. The air is entrapped within the outer gelatinous barrier, which facilitates floating and maintains relative integrity [39-40].

3. Bioadhesive systems:
Upon swallowing mucoadhesive polymers (like chitosan, HPMC, carbacol, lectin, CMC and Ion exchange resins) swells and adhers with mucous lining of GI tract. As bioadhesive coated system comes in contact with mucous layer, various specific or non specific interactions occur between the complimentary structures [40].

4. Magnetic systems:
Magnetic material is incorporated into small gastro retentive capsule which prevents from elimination of the drug from the stomach. Precision and accuracy of the magnet monitors their applicability and utility [41-42].

Table 2: Marketed Products of FDDS [43-45]

Sl. No.	Brand Name	Drug
1	Cifran OD	Ciprofloxacin
2	Modapar	Levodopa & Benserazide
3	Liquid Gavison	Alginic Acid & Sodium bicarbonate
4	Valrelease	Diazepam
5	Topalkan	Aluminium – Magnesium antacid
6	Cytotech	Misoprostol
7	Almagate Flat Coat	Antacid
8	Conviron	Ferrous Sulphate

Evaluation:

i) Evaluation of compression blend [45-46]:
Some characteristics of powdered blend may be affected by various process variables during mixing. The powdered blend properties are determined to interpret the flow property.

a) Angle of repose: Maximum angle possible between surface of the file of the powder and the horizontal plane. Frictional force in a granule powder can be determined by using fixed funnel method. The radius(r) of the base of the conical file is measured and calculated by using

$\text{Tan}\Theta = h/r$

Table 3: Pharmacopeial Specifications for Angle of Repose

Angle of repose	Type of flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very Poor

b) Bulk density: Defined as the mass of the powder divided by the bulk volume of the powder and expressed in gm/cm^3. It depends upon particle shape, particle size distribution and tendency of the particles to adher together and calculated by using

$$\text{Bulk density} = \frac{\text{Mass of the sample}}{\text{Apparent volume of the powder}}$$

c) Tapped density: Defined as the ratio of total mass of the powder to the tapped volume of the powder. The volume is measured by tapping the powder for 500 times, then for 750 times. The difference between 2 volumes should not be >2%, if it is more tapping is continued until the difference is <2%. It is expressed in gm/ml and calculated by using

$$\text{Tapped density} = \frac{\text{Mass of the sample}}{\text{Tapped volume of the powder}}$$

d) Compressibility index (Carr's index): It is used to measure flow of powder blend and also to determine inter particulate interactions between the powdered blend. It is determined from bulk density and tapped density. The difference between bulk density and tapped density is calculated by using;

$$\text{Carr's index} = \frac{\text{Bulk density} - \text{Tapped density}}{\text{Tapped density}} \times 100$$

Table 4: Pharmacopeial Specifications for Carr's Index

Carr's index	Type of flow
5 - 15	Excellent
12 - 16	Good
18 - 21	Fair
> 23	Poor

ii) Evaluation of compressed tablets [47-57]:

The prepared tizanidine HCL floating tablets are evaluated for their physicochemical properties

a) Weight variation: 10 tablets from each formulation are taken and their individual weight is determined. Then the average weight of the tablets is determined by using % deviation [47].

$$\% \text{ Deviation} = \frac{\text{Individual Weight} - \text{Average Weight}}{\text{Average Weight}} \times 100$$

b) Tablet thickness: 10 tablets are taken from each formulation and the thickness and diameter of each tablet is recorded by using digital Vernier callipers. The average thickness of the tablets in each formulation is then calculated by using standard deviation [48].

c) Tablet hardness: The resistance of the tablet to abrasion, chipping, breakage during handling, storage and transportation depends upon the hardness of the tablet. It is determined by using Monsanto hardness tester for each formulation and the average is calculated by using standard deviation.

Table 5: Pharmacopeial Specifications For Tablets Weight Variation

Average weight of tablets(mg) (1p)	Average weight of tablets(mg) (usp)	Maximum % difference
Less than 80	less than 130	10
80-250	130-324	7.5
More than 250	More than 324	5

d) Friability: Roche friabilator is used to measure the tablet strength. It contains plastic chamber that revolves around 100 rpm for 4mins. Tablets are reweighed to determine loss in the weight of tablets and are expressed in percentage.

$F\% = w0\text{-}w/wo \times 100$

Wo- Weight of the tablet before test

W- Weight of the tablet after test

e) Drug content estimation: 10 tablets are powdered; powder equivalent to 1 tablet is dissolved in 100ml of 0.1N Hcl buffer. The solution is centrifuged and supernatant fluid is collected. Finally, the drug content is estimated using UV-visble spectrophotometer at 320nm [49].

f) Floating test/ buoyancy: Tablets are placed in 0.1N Hcl in 100ml beaker and the time required to raise the tablet to the surface and float is determined as floating lag time [50-51].

g) Water uptake studies: Water uptake and dimensional changes of the dosage form are the measures to study swelling behaviour of the dosage form. It is studied by using USP dissolution apparatus II in 900ml distilled water maintained at 37◦± 0.5◦c and rotated at 50rpm. The tablets are withdrawn and weighed at selected time intervals. Swelling behaviour of the tablet is then calculated by [51].

%wo= wt-w0/w0×100

Wt - Weight of swollen tablet

W0- Weight of initial tablet

h) Dissolution studies: Drug release from floating tablets is determined by using usp type II paddle dissolution apparatus. The apparatus is filled with 900ml of 0.1N Hcl and the study is carried out at 37.5±0.5◦c and 50 rpm. 5ml of sample is withdrawn for every 12 hours and simultaneously replaced with same amount of fresh medium. The final absorbance is measured at 320nm using uv/v double beam spectrophotometer [52-53].

i) FITR studies: To study drug polymer interactions, samples of pure drug, dummy formulation and optimized formulation are analysed to observe characteristic peaks of the drug. If the intensity of the drug peak is decreased, it indicates that it is free from drug –excipient interactions [54].

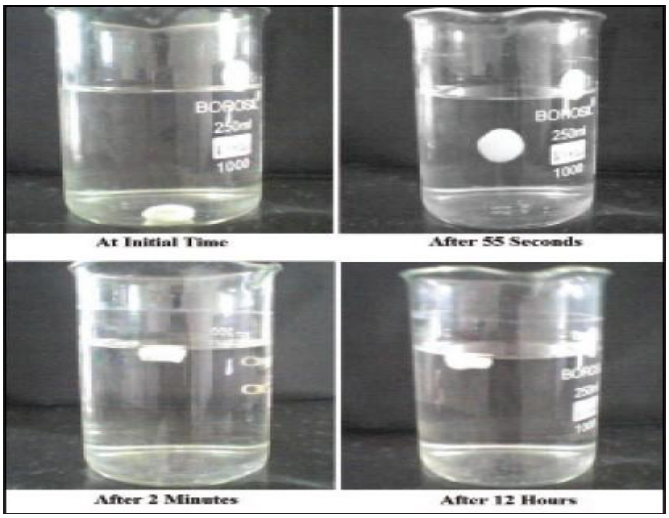

Figure 6: Invitro Dissolution Studies

j) Stability studies: Tablets are packed in (aluminium-aluminium) blister and placed in stability chamber for 1month. Then the samples are observed for colour change, roughness, bad odour, appearance of spots and fungal growth [55].

k) Invitro drug release: USP type II dissolution apparatus (paddle type) is used to determine the invitro drug release of the samples. 500 ml of dissolution medium is taken into dissoution flask maintained at 37 ± 0.5ºC and 100 rpm. One tablet is placed in each dissolution apparatus and observed for 24 hours. 10 ml sample is withdrawn for different time intervals and same quantity is then replaced with fresh dissolution medium. The collected samples are determined by using UV/V spectrophotometer [56-57].

APPLICATIONS OF FDDS [58-68]:

- ✓Sustained drug delivery system: Due to short residence time sustained drug absorption is not possible, whereas FDDS increases gastric residence time and remains in floating state in the stomach for several hours [58-59].

- ✓Site specific drug delivery: The drugs which are absorbed from the stomach produce local actions and target directly to the organ site, which reduces the dosing frequency [60].
- ✓Absorption enhancements: Due to site specific absorption from GIT, drugs show poor bioavailability. However, FDDS improves their absorption, and bioavailability [61-62].
- ✓Minimized adverse effects in the colon: The amount of drug that reaches the colon is reduced due to the retention of drug in the stomach. Thus, it prevents the adverse activity of drug in colon [63].
- ✓Used in the treatment of GI disease: FDDS prepared by calcium carbonate and gelling polymers (which acts as floating agent) are used for the treatment of gastric ulcers [64-65].
- ✓Reduced drug concentration fluctuations: FDDS minimizes blood drug concentration in the stomach, which ultimately minimizes the fluctuations of drug concentration [66].
- ✓Frequency of dosing: One dose of FDDS daily improves patient compliance and leads to controlled drug release within the stomach for prolonged period of time. Thus, frequency of dosing is reduced [67-68].

CONCLUSION

The present review gives an outlook of the development of effervescent floating drug delivery system of Tizanidine HCl using 2 different grades and concentrations of HPMC (k4m and k100m) by wet granulation method.

FDDS is an efficient and potential approach for gastric retention of dosage forms to improve bioavailability of Tizanidine HCl and to achieve controlled release for 12hours. The drugs with primary absorption in the upper GI tract are more advantageous in case of gastro retentive dosage form.

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