Research Article

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Oral Matrix Formulation for Floating drug Delivery System to Increase Gastric Retention time

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Gastro Retentive
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Abstract: All the pharmaceutical products formulated for systemic delivery via the oral route of administration, irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage form (solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology. The recent scientific and patented literature concluded that an increased interest in novel dosage forms which retained in the stomach for prolong and predictable period of time has been shown. It is a well known fact that differences in gastric physiology, such as, gastric pH and motility exhibit both intra as well as inters- subject variability demonstrating significant impact on gastric retention time and drug delivery behavior. Several approaches are currently utilized in the prolongation of the GRT including floating drug delivary systems, swelling and expanding systems, polymeric bio adhesive systems, high density systems, modified shape systems and other delayed gastric emptying devices. Floating dosage forms are emerging promising dosage forms. Floating dosage form can be prepared as tablets, capsules by adding suitable ingredients as well as by adding gas generating agent. In this review various techniques used in floating dosage forms along with current & recent development of stomach specific floating drug delivery system for gastro retention discussed.

Introduction

Oral drug delivery has been known for decades as the most widely used route of administration among all the routes that have been explored for the systemic delivery. All controlled release systems have limited applications if the systems cannot remain in the vicinity o f the absorption site. The controlled release drug delivery system posseing the ability of being retained in the stomach is called gastro retentive drug delivery system. They can help in optimizing the oral controlled delivery of drugs having absorption window continually releasing the drug prior to absorption window for prolonged period of time, thus ensuring optimal bioavailability[1]. The real issue in the development of oral controlled release dosage forms is not just to prolong the delivery of drugs for more than 12 hours, but to prolong the presence of the dosage forms in the stomach or upper gastrointestinal tract until all the drug is released for desire period of time. Rapid GI transit could result in incomplete drug release from the drug delivery device in the absorption zone leading to diminished efficacy of the administered dose[2]. Several approaches are currently used to prolong gastric retention time. These include floating drug delivery systems, also known as hydro dynamically balanced systems, swelling and expanding systems, polymeric bio adhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices[3,4]. Oral route is the most popular and convenient route for various drugs. Oral route generally consider an ideal drug delivery system that will possess two main properties:

a) It should be in a single dose for prolonging action.
b) It should be deliver the active drug directly to the target site.

These considerations have led to the development of a controlled or sustained delivery system. Sustained delivery describes a drug delivery system with delayed and/or prolonged release of drug.4,5. The main purpose for developing these systems is to enhance the safety of a product to extend its duration of action. There are many

disadvantages of these systems such as longer time to achieve therapeutic blood levels, more variation in bioavailability, enhanced first pass effect, and dose dumping. These systems are usually more expensive than the conventional systems6. Gastric residence time (GRT) is an important factor affecting the drug bioavailability of dosage forms.[7] Because of the short gastric emptying time, number of drug delivery systems are suffering with the low drug release in its absorption window that ultimately leads to scarce bioavailability of the administered dose. Gastro retentive systems are the current approach to overcome the above problem of GRT. Among the number of approaches floating drug delivery system (FDDS) is one of the promising delivery system which has a lower density than gastric fluids and thus remains buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating in the gastric content the drug is released slowly from the system at a desired rate which could leads to increase in absorption of drugs at their absorption window site.[8,9]Moreover FDDS is more suitable to those drugs that has absorption window in the stomach or in the upper small intestine.[10]

Materials and Methods

Materials:

Acyclovir is procured from Unichem Laboratories Ltd, Mumbai. sodium bicarbonate, Magnesium stearate, colloidal silicon dioxide, Mannitol, Citric acid monohydrate, polyethylene oxide, Eudragit RS100 are purchased from SD Fines chemicals Ltd Mumbai (India).

Methods:

METHOD OF PREPARATION:

Following were the steps involved in preparation of Floating tablet

1) Sifting of active material, polymers and excipients.
2) Dry mixing of step 1 ingredient.
3) Lubrication – sifting of lubricants and blending with dried granules of step 2.
4) Compression of lubricated granules of step 3.

Procedure:

Acyclovir floating tablets were prepared by direct compression method.

Acyclovir with various types of polymers was used to prolong the gastric residence time.

Sodium bicarbonate and citric acid were used as gas generating agent. The otherexcipient used was Micro crystalline cellulose for its diluent property.

Step No. 1. Sifting of active material, polymers and excipients

Accurately weighed quantity of Acyclovir, Mannitol, Sodium bicarbonate, citric acid and polymer Eudragit RS 100, were sifted through sieve no. 44.

Step No. 2. Dry mixing

Dry mixing was done in polybag for 15 minutes.

Step No. 3. Lubrication

i) **Sifting:** Weighed quantity of, colloidal anhydrous silica (Aerosil-200) was sifted through the sieve no. 40. Magnesium stearate was sifted through the sieve no. 60.

ii) **Blending:** Dried granules of the step no. 2 were blended with the sifted mix of step No.3 in polybag for 5 minutes.

Step No. 4. Compression

Lubricated powder blend was compressed to tablets on karnavati single punch machine by using 12 mm flat punch. The weight of tablet was adjusted to 500 mg and each tablet contained 200 mg acyclovir. The compressed tablets of each type of polymer were then evaluated for tablet characteristics such as thickness, weight variation and friability. Drug and the polymers are in the proportion of different concentrations and different formulations are prepared as mentioned in the Table No 1 .

Unit Formula:

Formulation code/ingredients	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)	F6(mg)	F7(mg)	F8(mg)	F9(mg)	F10(mg	F11(mg	F12(mg
Acyclovir	200	200	200	200	200	200	200	200	200	200	200	200
mannitol	152.6	127.6	102.6	77.6	52.6	27.6	152.6	127.6	102.6	77.6	52.6	27.6
sodium bicarbonate	20	20	20	20	20	20	20	20	20	20	20	
citric acid							20	20	20	20	20	
Eudragit RS 100	25	50	75	100	125	150	25	50	75	100	125	150
PEO	50	50	50	50	50	50						
sodium carboxy methyl cellulose							50	50	50	50	50	50
Magnesium stearate	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Aerosil	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
total	450	450	450	450	450	450	450	450	450	450	450	450

Evaluation of floating properties:

Preformulation studies

The floating tablets are evaluated for pre formulation and post formulation studies.

Micromeritic properties of microspheres

The floating microspheres are characterized by their micromeritic properties such as bulk density, compressibility index, Hausner's ratio and angle of repose8, 9.

Determination of Bulk Density, Tapped Density:15 grams of Drug-x was taken in 50 ml measuring cylinder which was placed in Electro lab Tapped Density Apparatus(method USP-I). Initial volume (V_0) of the cylinder was noted and then the cylinder was tapped 500 times and volume was measured. Then further an additional 750 tapings were repeated. No difference was noted between the volumes between two tapings (500 and 750). The final volume (V)was considered after completion of 750 taps. The values obtained are reported in the table

Compressibility Index and Hausner`s ratio : In recent years, the compressibility index and the closely related Hausner's ratio have become the simple, fast, and popular methods of predicting powder flow characteristics. The compressibility index has been proposed as an indirect measure of bulk density, size, shape, surface area, moisture content and cohesiveness of materials because all of these can influence the observed compressibility index. The compressibility index and the Hausner's ratio are determined by measuring both the bulk volume and tapped volume of a powder.

Flow Properties determination: Certain methods are used to measure granulation and powder characteristics in order to monitor granulation suitability for tableting. Good flow properties are essential for the transport of the material through the hopper into and through the feed frame and in to dies.

Angle of repose: The angle of repose was determined by the funnel method suggested by Newman. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose was calculated using the following formula

$$\tan \theta = h/r$$

Therefore, $\theta = \tan^{-1} (h/r)$

Where,

θ = Angle of repose

h = Height of the cone

r = Radius of the cone base

Post compression studies:

Tablet Dimensions:

Thickness and diameter were measured using a calibrated vernier calliper. Three tablets of each formulation were picked randomly and thickness was measured individually.11

Hardness:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester .It is expressed in kg/cm2. Three tablets were randomly picked and hardness of the tablets was determined.

Friability Test:

The friability of tablets was determined by using vergofriabilator. It is expressed in percentage (%). It is expressed in percentage (%). Ten tablets were initially weighed (wI) and transferred into friabilator .The friabilator was operated at 25rpm or run up to 100 revolutions. The tablets were weighed again (wF).The friability was then calculated by ---

%F=100(1-W I/W F)

% Friability of tablets less than 1% was considered acceptable.20

Weight variation Test:

Ten tablets were selected randomly from each batch and weighed individually to check for weight variation. A little variation was allowed in the weight of a tablet according to U.S. Pharmacopeia. The following percentage deviation in weight variation was allowed.

Floating Time Studies:

The buoyancy lag- time of the tablets was studied at 37±0.5 c, in 100 mlof 0.1N Hcl. The time required for the tablet to rise to the surface and float was taken as the buoyancy lag- time.The duration of floating is known as floating time.4

In Vitro dissolution studies For Acyclovir

Apparatus: Dissolution apparatus IP Type II (paddle)

Speed: 5o rpm

Min. temp: 37±0.5 0c

Sample preparation: One tablet each was placed in 6 – dissolution bowl. Then the apparatus was runned and the sample was withdrawn from each bowl at regular intervals and the solution was filtered through 0.45 micron memebrane filter. The filterate was collected after discarding first few ml of the filterate.11

Buffer: 0.1N Hcl

Preparation of 0.1N Hcl: Dissolve 8.5 ml of Hcl in 1000 ml of water.

Table No 1

Unit Formula:

Formulation code/ingredients	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)	F6(mg)	F7(mg)	F8(mg)	F9(mg)	F10(mg	F11(mg	F12(mg
Acyclovir	200	200	200	200	200	200	200	200	200	200	200	200
mannitol	152.6	127.6	102.6	77.6	52.6	27.6	152.6	127.6	102.6	77.6	52.6	27.6
sodium bicarbonate	20	20	20	20	20	20	20	20	20	20	20	
citric acid							20	20	20	20	20	
Eudragit RS 100	25	50	75	100	125	150	25	50	75	100	125	150
PEO	50	50	50	50	50	50						
sodium carboxy methyl cellulose							50	50	50	50	50	50
Magnesium stearate	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Aerosil	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
total	450	450	450	450	450	450	450	450	450	450	450	450

Preformulation studies:

Batch code	Bulk density	Tapped density	Carr's index	Hausners's ratio	Angle of repose
F1	0.475	0.565	16.03	1.19	25.45
F2	0.48	0.56	14.28	1.16	26.61
F3	0.451	0.565	20.17	1.25	27.34
F4	0.462	0.591	21.8	1.25	26.06
F5	0.469	0.561	21.39	1.19	25.42
F6	0.48	0.637	24.6	1.25	26.72
F7	0.45	0.55	18.18	1.22	29.42
F8	0.469	0.561	16.39	1.19	27.04
F9	0.48	0.637	24.6	1.25	26.72
F10	0.53	0.61	13.11	1.15	27.74
F11	0.49	0.56	12.5	1.14	27.51
F12	0.47	0.54	12.96	1.15	28.68

Post Formulation Studies

Hardness Results

Formulation code/Parameter	Hardness
F1	4.5
F2	4.5
F3	4.4
F4	4.4
F5	4.5
F6	4.6
F7	4.4
F8	4.5
F9	4.6
F10	4.5
F11	4.5
F12	4.5

Friability Results

Formulation code/Parameter	Friability
F1	0.23
F2	0.54
F3	0.61

F4	0.27
F5	0.12
F6	0.51
F7	0.29
F8	0.26
F9	0.11
F10	0.18
F11	0.24
F12	0.31

Floating lag time Results

Formulation code/Parameter	Floating lag time(mins)
F1	6
F2	7
F3	6
F4	8
F5	6
F6	8
F7	7
F8	7
F9	6
F10	11
F11	9
F12	6

Floating log time

Formulation code/Parameter	floating log time(mins)
F1	24
F2	24
F3	24
F4	24
F5	24
F6	24
F7	24
F8	24
F9	24
F10	24
F11	24
F12	24

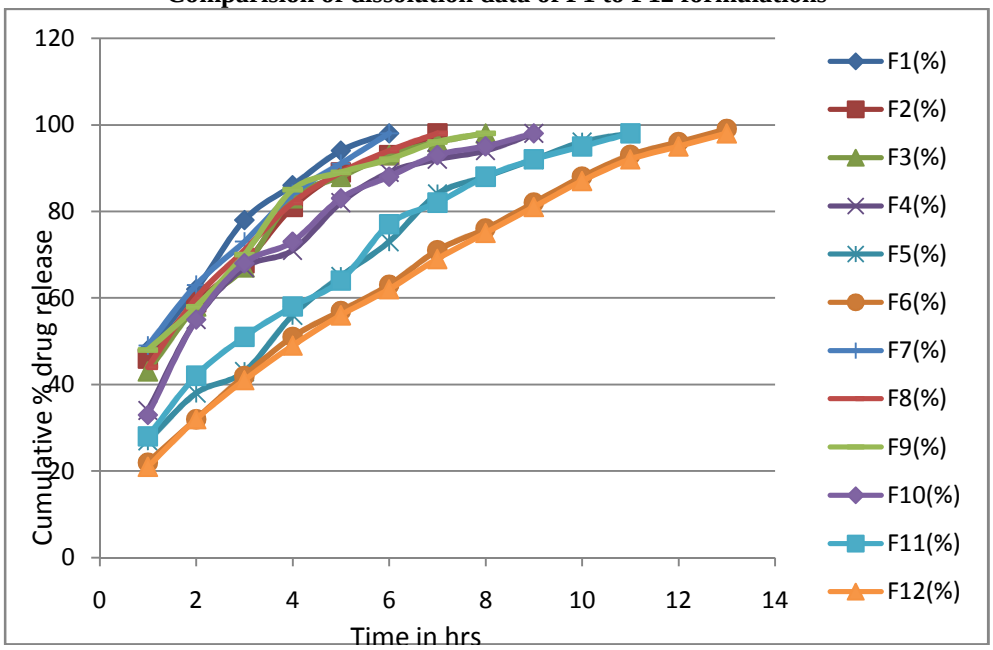
Content Uniformity

Formulation code/Parameter	Content uniformity
F1	99.65
F2	99.34
F3	98.34
F4	99.21
F5	100.34
F6	99.96
F7	99.23
F8	99.24
F9	100.02

F10	99.62
F11	99.45
F12	100.01

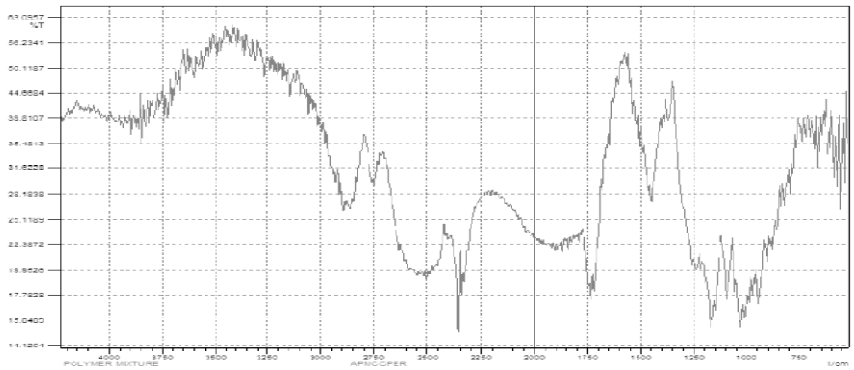
Formulation code/parameter	F1(%)	F2(%)	F3(%)	F4(%)	F5(%)	F6(%)	F7(%)	F8(%)	F9(%)	F10(%)	F11 (%)	F12(%)
1hr	48	46	43	34	27	22	49	44	48	33	28	21
2 hr	62	59	58	55	38	32	63	60	58	55	42	32
4 hr	78	68	67	67	43	42	73	71	70	68	51	41
6 hr	86	81	83	71	56	51	84	82	85	73	58	49
8 hr	94	89	88	82	65	57	91	89	89	83	64	56
10 hr	98	93	93	89	73	63	98	94	92	88	77	62
12 hr		98	96	92	84	71		98	96	93	82	69
14 hr			98	94	88	76			98	95	88	75
16 hr				98	92	82				98	92	81
18 hr					96	88					95	87
20 hr					98	99					98	97
22 hr												99
24 hr												98

Comparision of dissolution data of F1 to F12 formulations

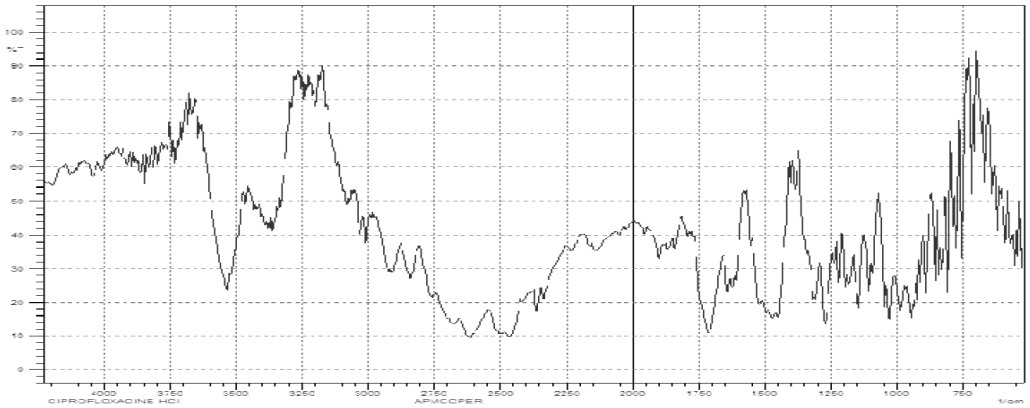


Results and Discussion

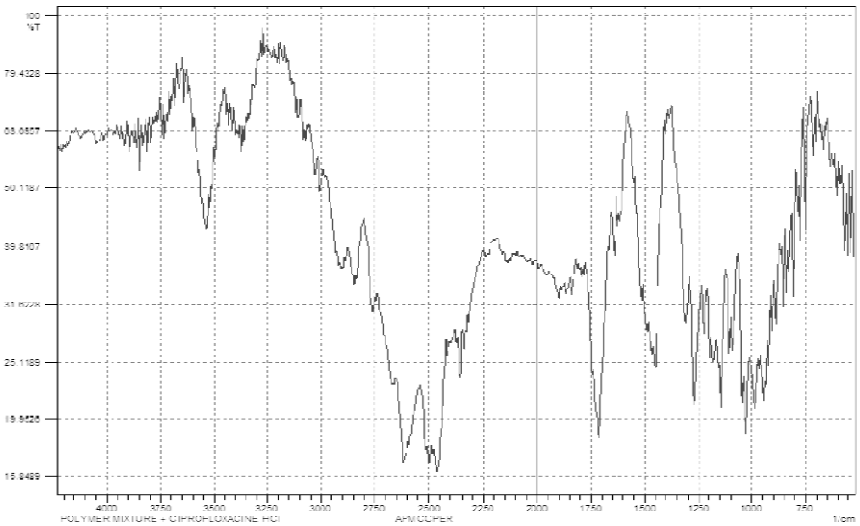
Drug – Excipient FT-IR studies: Fig No: 7



FT- IR Spectrum of Pure Acyclovir



FT-IR spectrum of polymer mixture (Microcrystalline cellulose, sodium starch glycolate, povidone, aerosil and other excipients. Fig No: 8



FT-IR spectrum of polymer mixture + Acyclovir.Fig No:9

Discussion

The drug and Excipients were studied for their Preformulation parameters and the granules were prepared by using different concentrations of binders and solvents. The prepared granules were thoroughly evaluated for their bulk density and tapped density. The optimization of Dry mixing time, Pre-lubrication time, Lubrication time and Compression force during the process at different time intervals was carried out and selection of appropriate time interval's for formation of granules and selection of suitable rpm for getting required range of hardness, thickness and disintegration time. The selection of suitable time interval for optimization based on granular consistency, LOD and %RSD values. The prepared tablets were characterized for thickness, weight variation, hardness and friability by following the procedures as per pharmacopoeia, to check the stability of tablets during transportation, packaging and storage. The results obtained in all the formulations were within pharmacopoeia standards. The results were tabulated.

References

1. Jagadle SC et al . Formulation and Evaluation of Gastrorentive Drug Delivery system of propranolanol Hydrochloride. AAPS Pharm Sci Tech, 2009.[cited 2011 Aug 10] 10 (3) 1071-1079.
2. Kavitha K ,Puneeth K.P .Tamil Mani T. *International j of Pharmtech research*. Vol 2 .**2010**, page 1662-1669.
3. Singh B, Kim K. *J Control Release*. **2000**;63: 235-259.
4. Chawla G, Bansal A. *Pharm Tech*. **2003**;27: 50-68.
5. Friend DR. Oral delivery: A new approach to dosage forms. Pharmaceutical News 2006; 9 : 375-80.
6. Robinson JR, Lee VHL. Controlled drug delivery: fundamentals and applications, Marcel Dekker: New York: 1978; 2 : 335- 410.

7. Brahmankar DM, Jaiswal SB. Biopharmaceutics and pharmacokinetics a treatise. New Delhi; Vallabh Prakashan: New Delhi : 1995; 1 : 10-48. Desai S, Bolton S. A floating controlled release drug delivery system: in vitro & invio evaluation. *Pharm Res*. 1993;10: 1321-1325.
8. Whitehead L, Fell JT. Collett JH, Sharma HL, and Smith AM. Floating dosage forms: an In vivo study demonstrating prolonged gastric retention. *J Control Release*. 1998;55: 3–12.
9. Singh BN, and Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. *J Control Release*. 2000; 63: 235– 259.