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# "A Review: Formulation Development And Evaluation Of Wax Incorporated Floating Beads Of Dasatinib"

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**ABSTRACT:**

The aim of the present study was to develop a floating drug delivery system using dasatinib. A multiple-unit gastroretentive sustain release drug delivery system of Dasatinib was developed from a completely aqueous environment, avoiding the use of any organic solvent, thus releasing the drug for a prolonged duration of time. Polyelectrolyte complexation technique was used to prepare beads.The beads with edible oil were prepare by mixing and homogenizing olive oil and water containing pectin and molten wax which was then extruded in to calcium chloride solution. The effects of carnauba wax on drug entrapment efficiency, floating lag time and morphology and drug release was studied. It was found that carnauba wax was sufficient to sustain the drug release at gastric pH. The results show that these beads can entrap drug in sufficient amount and also can successfully deliver the drug in stomach for a prolong duration of time avoiding the use of any organic solvent.

*Keywords : (Floating drug ,Gastroretentive ,Dasatinib , Carnauba wax )*

## INTRODUCTION:

Pharmaceutical dosage forms are drug delivery systems (DDS) by which drug molecules are delivered to sites of action within the body. Some common examples are tablets, capsules, suppositories, ointments, liquid, solutions, injections and transdermal patches. To achieve an optimum response from any dosage form, a drug should be delivered to its site of action at a rate and concentration that both minimize its side effects and maximize its therapeutic effects. The development of safe and effective drug dosage forms and delivery systems requires a thorough understanding of physicochemical properties that allow a drug to be formulated in to a pharmaceutical dosage form. Design of the appropriate dosage form or delivery system depends on the following factors:

a)Physicochemical properties of the drug, such as solubility, oil-to-water partition coefficient K(o/w), pKa value and molecular weight.

b)Dose of the drug.

c)Route of administration.

d)Type of DDS desired.

e)Pathologic condition to be treated.

f)Desired therapeutic effect.

g)Drug release from the delivery system.

h)Bioavailability of the drug at the absorption site.

i)Pharmacokinetics and pharmacodynamics of the drug.

Various routes of administrations play a marked role in the bio-availability of the active drug in the body. Oral route of administration is one of the oldest and most extensively used routes for the administration of drug providing convenient method of effectively achieving both local and systemic effect.

Various approaches are made in designing the formulations, which will overcome the disadvantages of conventional dosage forms, which include sustained/controlled release drug delivery system.[2]

## 1.1 Sustained Release Drug Delivery System

Drug delivery systems that are designed to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. Basic goal of the therapy to achieve steady state blood level that is therapeutically effective & nontoxic for an extended period of time.

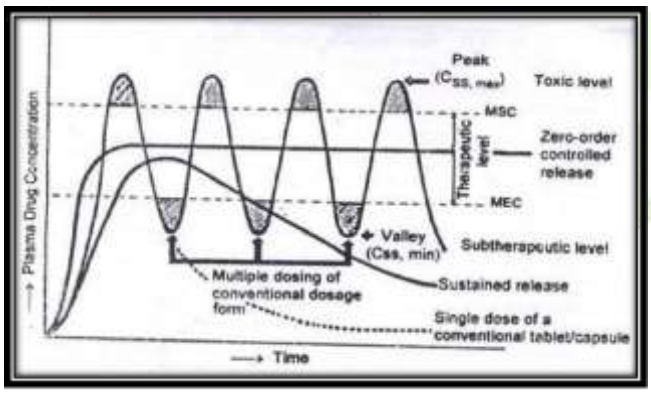


Fig. No. 1: A hypothetical plasma concentration- time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations.

There are the several reasons for the attractiveness of theses dosage forms. It is generally recognized that for many disease states, the goal in designing sustained or controlled delivery systems is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery. Numerous sustained release oral dosage forms such as membrane-controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed."

**Advantages of floating drug delivery system**.

a)Used for local action in the stomach.

b)In the treatment of peptic ulcer disease.

c)Used for the delivery of drugs with narrow absorption window in small intestine.

d)Reduced dosing frequency.

e)Improved bioavailability of drugs.

f)Used for drugs which are unstable in intestinal fluids.

g)Used to sustain the delivery of drug.

h)Used for maintaining the systemic drug concentration within therapeutic window.

i)Site specific drug delivery is also possible.

## Factors affecting floating drug delivery system.

**a)Density**:

Density of dosage form should be less than gastric content (1.004gm/ml)

**b)Size and Shape**:

Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT compared to those with a diameter of 9.9mm.The dosage for with a shape tetrahedron and ring shaped devices with flexural modulus of 48 and 22.5 kilopond per square inch (KSI) are reported to have better GIT for 90 to 100% retention at 24 hours compared with other shapes.

**c)Fed or Unfed state:**

Under fasting conditions, GI motility is characterized by periods of strong motor activity or migrating myoelectric complexes (MMC) sweeps undigested material from the stomach and if the timing of administration of the formulations coincides with that of the MMC, the GRT of unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

**d)Nature of the meal:**

Feeding of indigestible polymers of fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging the drug release.

**e)Caloric content**:

GRT can be increased between 4 to 10 hours with a meal that is high in proteins and fats.

**f)Frequency of feed:**

The GRT can increase by over 400 minutes when successive meals are given compared with single meals due to the low frequency of MMC.

**g)Gender:**

Mean ambulatory GRT in meals (3.4 ± 0.4 hours) is less compared with

their age and race-matched female counter parts (4.6 ± 1.2 hours), regardless of the weight, height and body surface.

**h)Age:**

Elderly people, especially those over 70 years have a significantly longer GRT.

**i)Posture:**

GRT can vary between supine and upright ambulatory states of the patients.Concomitant drug administration:

**j)Concomitant drug administration:**

Anticholinergic like atropine and propene, opiates like codeine and pro-kinetic agents like metoclopramide and cisapride.

## Mechanism of Floating system

Various attempts are made to obtain retention of dosage form in the stomach by increasing RT of stomach. These include introduction of different gastro retention dosage forms as floating systems (gas generating system and swelling and expanding system), muco-adhesive system, high density system, modified shape systems, gastric– emptying delaying devices and co administration of gastric empting delaying drugs. From this the floating drug delivery systems (FDDS) is most commonly used. FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolong period of time. When the system floats on gastric contents the drug is released slowly at the desire rate from the system. After the drug is released, the residue is emptied from the stomach. This results in increasing the gastric emptying time of stomach as well as controlling the fluctuations in PDC.

F = F Buoyancy–F gravity = (Df- Ds) gv… (1) Where,

F = Total vertical force.

DF = Fluid density.

DS = Object density.

V = Volume.

G = Acceleration due to gravity

Mechanism of Floating system

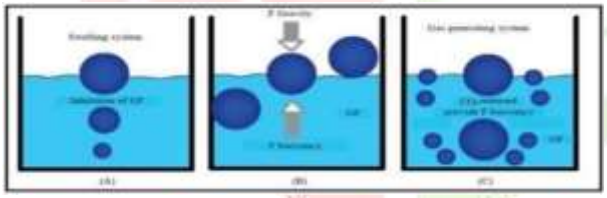

Fig. No.2: Mechanism of floating drug delivery

## Types of floating drug delivery system (FDDS) Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in the development of FDDS which are:

### 1. Effervescent systems

The main mechanism involved in this system is the production of carbon-di- oxide gas due to reaction between sodium bicarbonate, citric acid and tartaric acid. The gas produced results in the reduction of density of the system thereby making it to float on gastric fluids. These systems are further more classified as below; Volatile liquid containing systems: These are further categorized as;

A) Intra-gastric floating gastro intestinal drug delivery system

B) Inflatable gastrointestinal delivery system

C) Intra-gastric – osmotically controlled drug delivery system

D) Matrix tablets

E) Gas generating systems

i. Floating capsules ii. Floating pills iii. Floating systems with ion exchange resins

**2 Non- effervescent systems**

These are a type of floating Gastroretentive drug delivery system in which gel forming hydrocolloids, polysaccharides and matrix forming polymers like polycarbonates, polystyrene, polymethacrylates etc. are used. These are further classified as follows,

a) Hydro-dynamically balanced system

b) Micro-balloons/ hollow microspheres

**TYPES OF GASTRORETENTIVE BEADS**

**1 Effervescent Beads**

**2 Non- Effervescent system**

i. Calcium alginate / pectinate beads

ii. Alginate beads with air compartment

iii. Casein-gelatin floating beads

**3 Layered Tablets:**

i. Single layered floating tablets

ii. Bi-layered floating tablet

**Techniques For Preparing Gastroretentive Beads:**

a) Jet cutting method

b) Resonance method

c) Electrostatic method

e) Method of siepmann

f) Ion gelation emulsion method

g) Ionotropic gelation method

h) Polyelectrolyte complexation technique

**POLYELECTROLYTE COMPLEXATION TECHNIQUE**

The quality of hydrogel bead sprepared by ionotropic gelation method can also be enhanced by using polyelectrolyte complexation technique. The mechanical strength and permeability barrier of hydrogels can be enhanced by the addition of oppositely charged another polyelectrolyte to the ionotropically gelated hydrogel beads. For instance, addition of polycations allows a membrane of polyelectrolyte complex to form on the surface of alginate beads. Large numbers of natural and chemically modified polyelectrolytes have been investigated and a schematic diagram of the preparation of hydrogel beads through ionotropic gelation and polyelectrolyte complexation is shown in below.

Polyelectrolyte solution [alginate (-)/Gellun gum (-)/CMC (-) + Drug] 5% HPMC phthalate as a coating material

Added drop wise under magnetic stirring by 21 G needle

Calcium chloride solution (+) Chitosan solution (+) Hydrogel bead

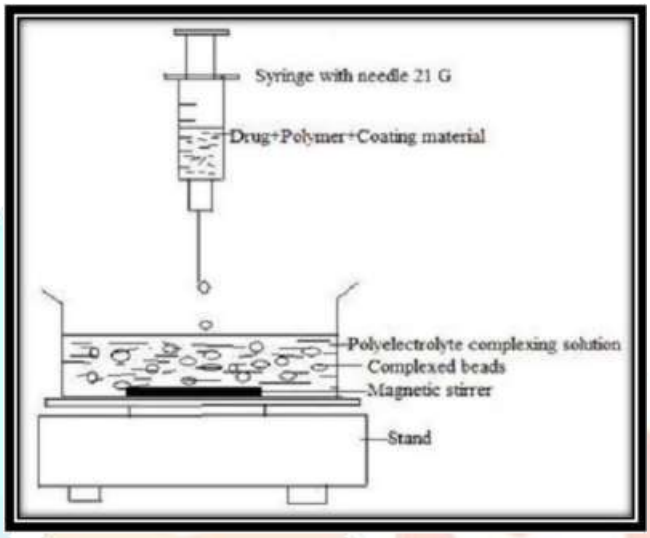


Fig.No.3: Schematic diagram of the preparation of hydrogel beads by ionotropic relation and polyelectrolyte complexation

## OBJECTIVES:

Formulation and development of stomach specific drug delivery of Dasatinib by using floating pectinate wax beads as a drug candidate which remain in the stomach and upper part of GI tract prolonged period of time and there by controlled the drug release at the desired site within stipulated time.

The above explored study for present content is divided into the following objectives.

a)To carry out preformulation study of drug and polymers.

b)To perform compatibility study between drug and polymer.

c)To prepare stomach specific floating wax beads using polymers.

d)To study the sustained release of stomach specific floating wax beads of Dasatinib.

e)To study the evaluation of prepared stomach specific floating wax beads of Dasatinib.

f)To carry out the stability study of the prepared stomach floating wax beads

## Material

Materials used for experimental work are :-

Dasatinib ,Pectin ,Carnauba wax ,Olive oil ,Calcium chloride ,Methanol AR ,Potassium Dihydrogen Phosphate ,Disodium Hydrogen Phosphate ,Hydrochloric acid ,Sodium Hydroxide ,Distilled water+

**Composition of formulation** :

Table No. 1: Composition of formulation:

| code | Drug | Pectin | Olive oil | Carnauba Wax | Water (Q.S) |
|---|---|---|---|---|---|
| F1 | 300 | 4 | 30 | 4 | 100 |
| F2 | 300 | 4 | 30 | 1 | 100 |
| F3 | 300 | 4 | 30 | 12 | 100 |
| F4 | 300 | 4 | 30 | 16 | 100 |

The following steps were carried for its preparation:

Step 1. Emulsion of pectin, olive oil and drug was prepared in the distilled water using the high speed homogeniser at 3000 RPM for 15 min.

Step 2. The pre-weighed amount of wax was melted in the porcelain dish on the heating water bath.

Step 3. The emulsion formed was heated to the temperature above the melting point of the wax.

Step 4. The molten wax was dispersed in the preheated emulsion using hot plate with magnetic stirrer.

Step 5. After stirring for 15 min the above solution was filled into the 22G syringe and air bubbles were removed.

Step 6. The solution was added drop wise into the calcium chloride solution.

Step 7. After addition of solution the beads are formed. The beaker was kept aside for 15 min.

Step 8. The beads were filtered from calcium chloride solution. The beads were rinsed thoroughly with distilled water and dried at room temperature

**Evaluation of floating wax beads**

**1 . Physical Appearance**

To developed formulation, dissolve all the pre-requisite to become a floating wax beads system and floated instantaneously at pH condition of the stomach.


**Fig. No. 4: Physical appearance of the formulated beads**

**Micromeritic properties**

The micromeritic properties (Bulk density, Tapped density, Carr's index, Hausner's ratio) of all the formulated batches was measured.

Table No.2: Micromeritic properties of the formulation

| Batch code | Bulk density (gm/ml) ±SD | Tab density (gm/ml) ±SD | Carrs index ±SD | Hausners ratio ±SD |
|---|---|---|---|---|
| F1 | 0.3920+0.0013 | 0.4693+0.0021 | 11.70+0.0578 | 1.1904+0.0085 |
| F2 | 0.4804+0.0045 | 0.5563+0.0049 | 6.67+0.0357 | 1.1277+0.0010 |
| F3 | 0.4312+0.0020 | 0.5182+0.0016 | 9.22+0.0441 | 1.1834+0.0058 |
| F4 | 0.3604+0.0011 | 0.4569+0.0025 | 8.10+0.0482 | 1.2658+0.0011 |

From the study of the micromeritic properties of the formulation it was found that the bulk density of the formulation lies within range of 0.3604 – 0.4804 g/cm3, tapped density within range of 0.5563- 0.4569. The Carr's index lies within range of 6.76 – 11.70 and Hausner's ratio within range of 1.2658 – 1.1277 which indicates that the prepared formulation have excellent flow property.

**3.Percentage yield**

The percentage yield of floating beads of Dasatinib was measured.

Table No. 3: Percentage yield of the formulations

| Sr. No. | Batch Code | Percentage Yield (%) |
|---|---|---|
| 1 | F1 | 96.84 |
| 2 | F2 | 97.14 |
| 3 | F3 | 95.65 |
| 4 | F4 | 95.20 |

All formulations F1 – F4 found percentage yield 97.14 – 95.20% which lied in the normal range in table no.3

**4. Drug content and drug entrapment efficiency**

The floating beads were dissolved in 0.1N Hydrochloric acid under sonication and filtered. The drug content was assayed using UV- spectrophotometer( V630, Shimadzu Co Ltd., Japan) at 262nm after suitable dilution with 0.1N Hydrochloric acid. Percentage drug content and percentage entrapment efficiency was determined using formula :

$$\%\text{Drug content} = \frac{\text{Actual drug content}}{\text{Total amount of drug taken}} \times 100$$

$$\%\ \text{Drug entrapment of efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

Table No. 4: Drug content of the formulation

| Sr. No. | Batch Code | Contents(%)±SD |
|---|---|---|
| 1 | F1 | 96.81± 0.2743 |
| 2 | F2 | 96.89 ± 0.8369 |
| 3 | F3 | 96.22 ± 0.7968 |
| 4 | F4 | 95.21 ± 0.5750 |

The percentage drug content of all prepared formulations was found to be in the range of 95.21 – 96.89%. Therefore uniformity of drug content was maintained in all formulations.

Table No. 5: Drug entrapment efficiency of formulations

| Sr. No. | Batch Code | % DEE± SD |
|---|---|---|
| 1 | F1 | 90.21 ± 0.6552 |
| 2 | F2 | 92.21 ± 0.6864 |
| 3 | F3 | 88.36 ± 0.6251 |
| 4 | F4 | 88.06 ± 0.8489 |
| | | |

The percentage drug entrapment efficiency of all prepared formulations was found to be in the range of 88.06% - 92.21%. Therefore entrapment efficiency was found to be less due to the diffusion of the drug into the calcium chloride solution during the formation of the beads.

**5.Floating lag time and floating time**

The gel beads samples (n=20) were placed in the beaker filled with 50ml of 0.1 N HCl (pH 1.2) solution. Temperature was maintained at 370C. The floating time of beads was observed for 20hrs. The preparation was considered to have buoyancy in the test solution only when all the gel beads floated in it. The time that formulation took to emerge on the medium surface (floating lag time) and time the formulation constantly floated on the dissolution medium surface (floating time) were noted.

Table No. 6: Floating lag time and floating time of formulations

| Sr.No. | Batch Code | Floating lag time (min) | Floating Time(hrs) |
|---|---|---|---|
| 1 | F1 | 1.37 ±0.4630 | >12 |
| 2 | F2 | 1.12 ± 0.09391 | >12 |
| 3 | F3 | 1.21 ± 0.00707 | >12 |
| 4 | F4 | 1.25 ± 0.04221 | >12 |

The above table showed floating lag time in the range of 1.12 – 1.37 min. and floating time >12hr for all formulations F1-F4. This is due the increase in the concentration of the carnauba wax.

**6. Swelling studies**

Beads were studied for their swelling characteristics. Only those batches were selected which have good drug content and entrapment efficiency more than 50%. Sample from drug loaded beads were taken, weighed and placed in wire basket of USP dissolution apparatus II. The basket containing beads were put in a beaker containing 100ml of 0.1N HCl (pH 1.2) maintained at 370C. The beads were periodically removed at predetermined intervals and weighed. Then swelling ratio was calculated as per following formula:

$$\text{Swelling index} = \frac{Ws - Wo}{Wo} \times 100$$

Where, Ws = weight of swollen beads,

Wo = weight of dried beads

Table No. 7: Swelling Index of formulations

| Sr. No. | Batch Code | Swelling ± SD |
|---|---|---|
| 1 | F1 | 15.68 ± 0.02471 |
| 2 | F2 | 20.66 ± 0.05241 |
| 3 | F3 | 14.66 ± 0.0254 |
| 4 | F4 | 10.25 ± 0.01679 |

For all prepared batches (F1-F4), percent swelling ratio was found to be in the range of 10 – 20.66 %. The F2 batch showed the maximum swelling index. This is because of the lipophillic nature of the carnauba wax which affected the swelling of the beads.

**7. Particle size determination**

The particle size of all beads was determined by the dry state using the optical microscopy method.

Table No. 8: Particle size determination of formulation

| Sr. No. | Batch Code | Particle size (mm) ± SD |
|---|---|---|
| 1 | F1 | 1.51 ± 0.0251 |
| 2 | F2 | 1.21 ± 0.0163 |
| 3 | F3 | 1.46 ± 0.0258 |
| 4 | F4 | 1.27 ± 0.0355 |

For F1-F4 batches average particle size was found to be in the range of 1.21 - 1.51 mm.

**8. Surface characterization**

Surface characterization of the beads were examined with scanning electron microscopy. The SEM result showed that the particle size of formulation was found to have regular and spherical shape with rough and uneven surface.

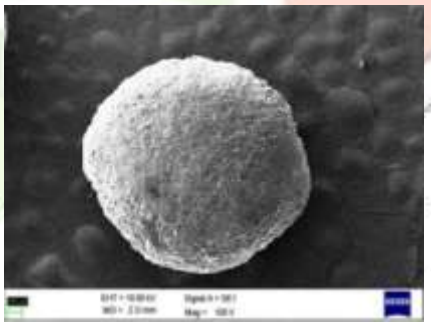

Fig. No.5: Surface morphology of the formulation

**9.Differential Scanning Calorimetric studies**

Dasatinib was compatible with polymer. There is slightly peak broadening in physical mixture of polymer to pure Dasatinib.

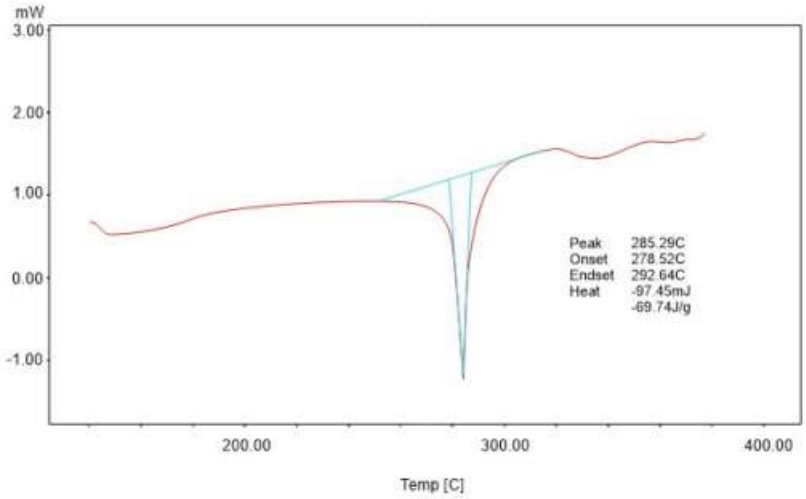


Fig. No.5: DSC thermogram of formulation

From the above observation from FTIR and DSC study, it was concluded that polymer and drug did not interact with each other and are compatible.

## REFERENCE


1. Dick RG, James CE III. The APhA, Complete Review for Pharmacy [internet].9th ed. Washington, Mahato RI; Chapter 3, Dosage Forms and Drug Delivery Systems.
2. Gennaro AR. Remington: The science and Practice of Pharmacy, 19th ed. Volume II. Easton, Pennsylvania: Mack publishing company;1995:Chapter 94, Sustained Release Drug Delivery Systems; pp. 1660 – 75.
3. Bhowmik D. et.al. (2009), Floating drug delivery system- A review, Der Pharmacia Letter; 1:pp.199-218
4. Vyas SP, Khar RK,(2012), Controlled drug delivery: Concepts and Advances, 2nd edition VallabhPrakashan , Balaji offset printers Delhi, MK Jain:pp196-217
5. Joshi R, Mukhopadhyay S.(2014), Review on Floating Drug Delivery system International Journal of Pharmaceutical Archive; 3: 424 – 438
6. Narang N.(2011), An Updated Review on: Floating Drug Delivery System. International Journal of Applied Pharmaceutics; 3:pp.1-7
7. Shukla S. et.al(2011), A Review On: Recent Advancement Of Stomach Specific Drug Delivery System. International Journal Of Pharmaceutical and Biological Archive, ;2(6): pp.1561-1568
8. Venkateshwara Rao KL et.al. (2016), Recent advances in Gastroretentive drug delivery system. International journal of pharmaceutical sciences and technology; 9(3):pp. 3227.
9. Pornsak Sriamornsak et.al.(2008), Wax-incorporated Emulsion Gel Beads of Calcium Pectinate for Intragastric Floating Drug Delivery, AAPS PharmaSciTech; 9(2),pp.571-578
10. Kush Biswas et.al.(2023), A Review on floating drug Delivery system International of Pharmaceutical Drug Design , Vol-1,Issue-1.
11. Vinod Sarpa Vasave (2023),A Review on floating Drug Delivery system World Journal Of Pharmaceutical Research, ISSN 2277-7105

12. Raymand C Rowe, Paul J Sheskey, Sian C Owen , Handbook of Pharmaceutical

13. Excipients, 5th edition, Published by Pharmacutical Press, pp.498500,507,508,809,810.

14. CH. Madhumathi, M. Padmalata, Sneha Development and Validation of uv spectroscopic method for the estimation of Carvedilol in tablet IJIPSR

15. Vijay Chudiwal et.al.(2017), Innovative Technologies for Gastro-retentive Drug Delivery Systems, Asian Journal of Pharmaceutical Education and Research; 6(4),pp. 20-28

16. Ritesh Kumar et.al. (2017), Adavanced Multiple unit Controlled release floating beads: A Review, World Journal of Pharmaceutical Research, 6(15),pp.238-259.

17. Bairagi PD. et. al. (2018),Formulation development and evaluation of floating wax microspheres of Tizanidine Hydrochloride: Asian Journal of Pharmacy and Pharmacology 2018,4(5),pp. 673-679.

18. Sitthiphong Soradech et.al.(2016), Development of Wax incorporated Emulsion Gel beads for the Encapsulation and Intragastric floating Delivery of the Active Antioxidant from Tamarindus indica L., Molecules, 21,pp. 380; doi:10.3390/molecules2103038

19. Bairagi P. D. et.al. (2018), Floating Beads As A Magical Drug Carrier: A Review,Asian Journal of Pharmaceutical Education and Research,7(2):pp 482-510

20. Ujjwala Kandekar et,al.(2014), Preparation and Evaluation of Wax micro particulate for Sustained Release Drug delivery system, Researh and reviews: Journal of Pharmaceutics And Nanotechnology;2(1),pp.31-36

21. Nevine Malak (2012), Formulation of Coated polymer reinforced gellan gum beads of Tizanidine HCl using Fractional Factorial Design, International Journal of Pharmacy and Pharmaceutical Sciences;4(5).pp.369-379.

22. Bakan JA, Anderson JL (1986), Microencapsulation part III, through Lachmann L, Liberman HA, Kanig JL. The theory and practice of Industrial Pharmacy, 2nd-ed.,Varghese Publishing House, Bombay.pp. 428.

23. Venkatesh Gavini et.al.(2014), Formulation & in-vitro evaluation of Wax incorporated Floating Beads of Silymarin, International Journal of PharmaTec Research;6(6),pp.1824-1832.

24. Parmar PD et.al.(2014), Floating drug delivery system: A Novel approach to prolong the gastric retention, World Journal of Pharmacy and Pharmaceutical Sciences;3(4),pp.418- 444

25. MD.Afrose Soha et.al.(2021) A Review on Floating Drug Delivery system International Journal of Research in Pharmacy and Chemistry,ISSN No. 2231-2781

26. Yashavanth.C. et.al.(2022), A Review on Floating Drug Delivery System International Journal of Advanced Research,ISSN No. 2320-5407