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Formulation and Evaluation of Gastro retentive floating microspheres of pioglitazone in the treatment of diabetes

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ABSTRACT

The key obstacle in the process of developing a system for the oral administration of a drug is not only to maintain the drug release but also to lengthen the presence of the dosage form within the gastrointestinal tract until the entire drug is released at the desired rate and in the desired amount of time. The goal of the floating microspheres is to increase the amount of time that gastric retention is achieved. Floating drug delivery systems have a smaller bulk thickness than gastric juice and are able to keep floating on gastric juice for an extended period of time without affecting the rate at which the stomach empties, hence boosting bioavailability. There are many different dose forms available for gastro retentive medications, such as tablets, capsules, pills, laminated films, floating microspheres, granules, and powders. The homogeneous distribution of these multiple-unit dosage forms in the stomach, which results in more repeatable drug absorption and lower risk of local discomfort, has brought a lot of attention to floating microspheres recently. The goal of this review is to compile contemporary research on the method of production, as well as the numerous aspects that affect the performance and characterisation of floating microspheres, and present that information in an organized fashion.

KEYWORDS: Floating Microspheres, Approaches, Polymer, Mechanism, Methods

INTRODUCTION

It is generally agreed that oral administration is the safest and most effective method, and it is also the route that is utilized the most. To treat a variety of medical conditions, oral sustained release delivery systems are frequently utilized. However, sustained release dosage forms frequently run into the problem of rapid gastrointestinal transit, which can lead to partial absorption of medications that are absorbed from the top section of the gut. This is a common

issue with these forms of medication. The acronym GRDDS stands for "gastro-retentive drug delivery systems," which refers to formulations that have a gastric-retentive behavior. Floating microspheres are a type of GRDDS that consist of numerous units that make it possible to deliver a medicine to the site of absorption over an extended period of time. The method of floating medicine administration has a bulk thickness that is less than GI fluid, and as a result, it maintains buoyancy in the abdomen for an extended period of time without affecting the rate at which the stomach empties. During this procedure, the substance is allowed to float, and then its release from the system is postponed so that it can occur at the optimal rate after the medicine has been distributed. This increases the likelihood that germs will invade the body and leads to effective regulation of the amounts of bacteria-killing drugs in the body. Because of this, the amount of time that medications spend in the stomach is considerably increased when gastroretentive systems are used. These systems can remain in the stomach for several hours. The inter-subject variability and the so-called "peak and valley" effect can be reduced by increasing the gastric residence time (GRT) of a rate-controlled oral drug delivery system. This leads to increased predictability and bioavailability of the dosage form, particularly for molecules that have a narrow absorption window. In addition to this, the total amount of time that food passes through the digestive tract is increased. As a result, the number of dosing regimens that need to be followed can be decreased, and the solubility of medications that are less soluble in an environment with a high pH can be enhanced.Oral controlled drug delivery mechanisms are becoming more popular as a solution to these challenges since they release the drug into the GIT over extended periods of time and maintain a constant concentration of medication in the blood. In the gastric region, the gastroretentive dose type may continue for fewhours and therefore greatly raise the drug's GRT in order to improve bioavailability, reduce the amount of drug waste, and improve the solubility of medications with low solubility.

MATERIAL AND METHODS

Collection of Drug and Excipients:

In order to conduct research work on this topic, there was need to procure drug piogilatazone and polymers as coating material. These polymers included Eudragit S100, HPMC, DCM+ Ethanol was chosen as co-polymer because the method of preparation was determined to be “Emulsion Solvent Evaporation Technique”.

Pre-formulation studies

Pre-formulation itself implies the need to carry out studies before formulating a dosage form. The need for this approach lies in the reason because it is very important that the API and excipients that will come together to form dosage form must be compatible with each other. This is done to ensure that no problem arises in stability testing in future and dosage form remains stable throughout its shelf life.

Solubility testing:

Solubility of drug was detected in water, methanol , ethanol, DMSO . A saturated amount of sample drug was dissolved in different soluble media. After interacting with various solvent the dispersion/ solution was filtered using

Whatman Filter Paper. Later in order to check solubility UV Spectroscopy was employed and drug content was calculated by plotting standard curve against concentration.

Compatibility test:

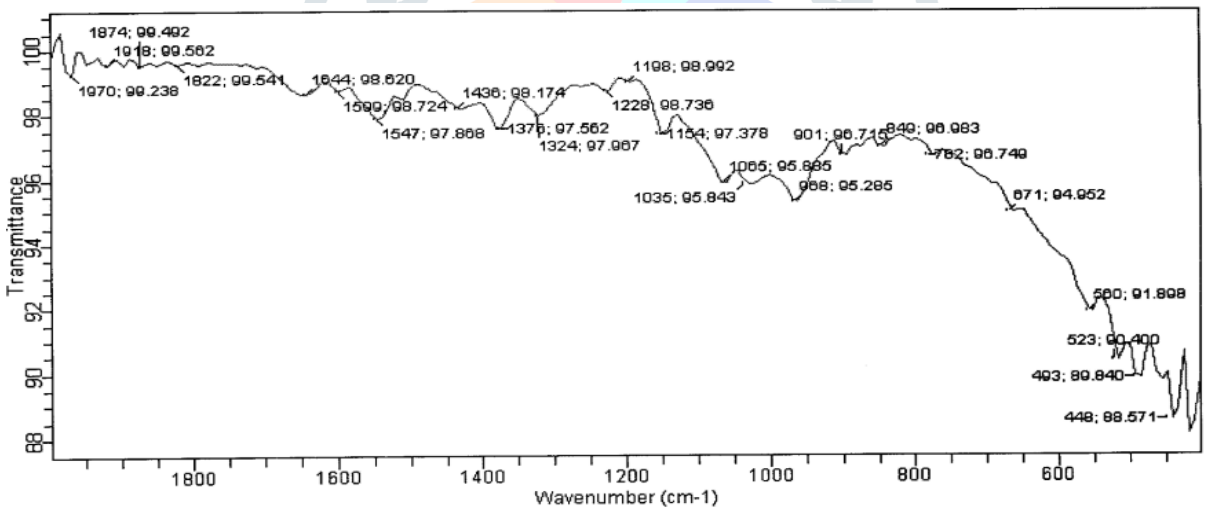
Compatibility studies between the API and the polymers (Eudragit S100, HPMC) was done to ensure these species do not interact with each other and cause incompatibility in the final formulation.

Melting Point Determination:

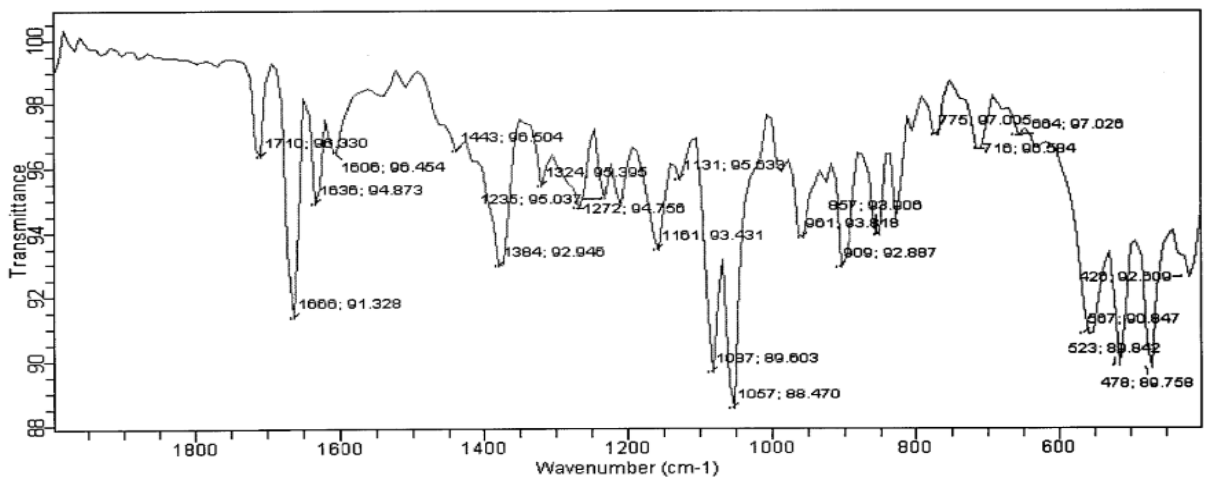
Melting point of main API was checked and co-related with standard to check its purity and saturation level. The melting point was checked thrice to avoid any sort of error in recording it.

FTIR:

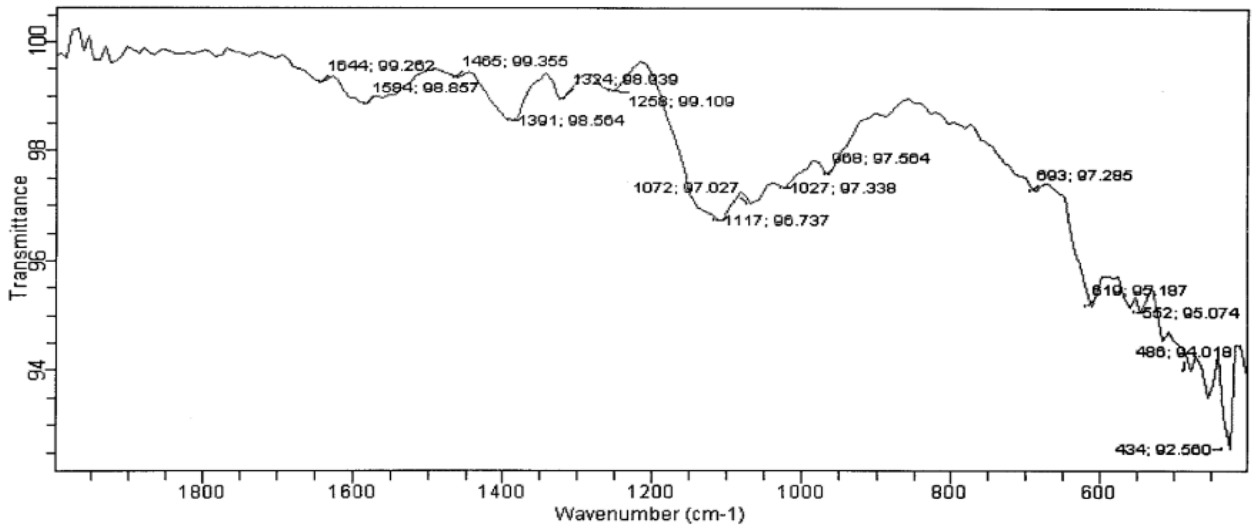
FTIR studies is usually employed to study the compatibility between the interacting species. In this case drug, polymers (Eudragit S100, HPMC) was kept together in a container in powdered natural form for months. After sufficient period of time, they were checked for compatibility and interaction if any. This was done using the FTIR Technology Method. The sample was run 4000 cm^{-1} -400 cm^{-1}. Any shift in the peaks were recorded and interaction among these materials were noted.



FTIR spectra of HPMC and pure drug(pioglitazone)



FTIR spectra of Pioglitazone



FTIR spectra of pure drug (Pioglitazone) and Eudragit S100

Preparation and Development floating Microspheres

The concept behind this novel drug delivery system was to design and fabricate a dosage form which will last for longer time at the site of application, to provide a continuous exposure and action. So to make such dosage form, various methods were studied and reviewed. Among all the methods available for the fabrication of Floating Microspheres, "Emulsion Solvent Evaporation Technique" was choosing best fit for this project work. In this methodology, the comparison was done by using 2 different origin polymers. Since this method requires crosslinking process so, Tween 80 was used to crosslink the Microspheres. The vehicle used here is distilled water. Below here is procedure mentioned to formulate floating microspheres of Pioglitazone [8,18,27,47,54,60]

i. Floating microspheres were prepared by emulsification (o/w) solvent evaporation method using a varying concentration of polymers (HPMC, Eudragit S100).

ii. The polymer solution was prepared by dissolving polymers (HPMC, EudragitS100) in different ratio of the mixture of solvents (ethanol, dichloromethane) with vigorous shaking.

iii. The aqueous solution containing tween80 was taken in another beaker.

iv. The polymer solution was then added manually dropwise into the aqueous solution through a syringe (22gauge) under continuous stirring at 100rpm.

v. The formed microspheres were collected and washed with distilled water 2-3 times and dried at room temperature for 24 hours.

Evaluation of formed dosage form

Below are the lists of various parameters chosen for the evaluation of microspheres:

Physical appearance and morphological characteristics: the microspheres that were formulated were analyzed for its physical appearance, its shape and size. Random choosing of microspheres were done, among all of them around 100 pieces of them were took out from each batch of preparations. All the selected particulate matter was checked by taking it through a ocular microscope attached with a calibrated stage micro ruler. This was done to estimate the size of microspheres and it was carried out with the help of naked eye.

Scanning Electron Microscopy: the exterior surface morphological characteristics of microspheres were gauged with the assistance of scanning electron microscopy method. In this SEM testing process, the microspheres to be tested are initially dried so that they do not consist of any moisture in it. Later sample were prepared by mounting the sample onto a metal stub with adhesive tape is applied on the both sides so that the matter on it does not fall. Carbon coating was done in a high vacuum evaporator. Then the process of scanning and taking images was done.

Drug entrapment efficiency: it gives an estimation of the percentage of drug entrapped by the microspheres. It is calculated by taking 15mg of microspheres, and dissolving it in 50ml of acetone. This media was shaken continuously rigorously, and aliquots were taken in a particular concentration and volume of media was replaced with sufficient amount of acetone (2,4,6,8,10,12µg/ml). This aliquot was analyzed using the UV visible spectroscopy. It is calculated using the formula,

Drug entrapment efficiency (%): A.C / T.C X 100,

Where, A.C = Actual content of drug T.C = Theoretical content of drug

Percentage yield: the percentage yield helps to get an idea about the proficiency in making microspheres. It gives an estimate to how to calculate the amount of ingredients used to the amount of dosage form being prepared. It is calculated using the formula.

$$\textbf{Percentage yield} = \frac{\textbf{Weight of dried microspheres} \times 100}{\textbf{Weight of drug + weight of polymer}}$$

Swelling capacity: As the medium of action here is Bio adhesion so it is essential to study its swelling capacity rate. This evaluation parameter gives an idea regarding how good is our polymers in holding the water and adhering to Mucosal Membrane. It is generally calculated by taking some fixed amount of dosage form and weighing them initially, then soaking it in some buffer solution (Phosphate Buffer pH6.8). After an interval of every 1 hour, these Microspheres are weighed again to analyze addition in their weight if any, is recorded.

***In vitro* studies**: this test as the name implies gives an idea regarding the concentration of dosage form in a particular media in a particular time. This test is carried in USP dissolution test apparatus. In this assembly, around 900ml of dissolution fluid is filled which is generally a Phosphate Buffer Solution of pH 6-6.8. A proper weighed amount of dosage form is taken and dissolved in above media. This assembly is kept at a uniform temperature not exceeding 37.5˚C. After dissolution apparatus is switched on, at regular interval of time around 5ml of aliquots is removed and the removed solution is replaced by fresh Phosphate Buffer Media. The aliquots that was removed initially was checked for its concentration with the help of UV Visible Spectroscopy Technique at a wavelength of 289nm. This parameter keeps an eye on the release pattern of drug from dosage forms.

Stability studies testing (According to ICH guidelines)

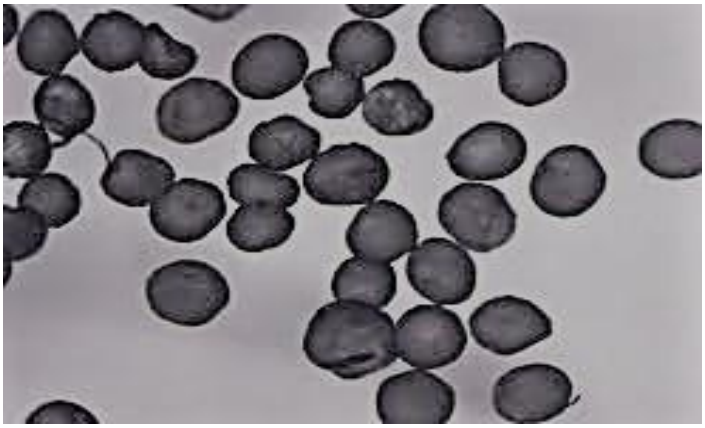
Accelerated stability studies was of prime importance to be carried out on the optimised formula. This study was carried out under the guidelines of ICH (Q1A). this stability studies data was calculated for 30, 60, 90 days. The parameters for its assessment were temperature, moisture, light, relative humidity. After keeping the optimised formulation under a fixed period of time, the evaluation parameter studies mentioned above were once again carried on these formulations so as to be satisfactory of its compatibility, stability, shelf life maintenance in the long run.

RESULTS

Physical appearance and morphological characteristics:

Particle size distribution of microspheres by optical microscope

Sr. No.	FORMULA CODE	AVERAGE PARTICLE SIZE (µm)
1	F1	24
2	F2	22
3	F3	29
4	F4	31
5	F5	34
6	F6	36



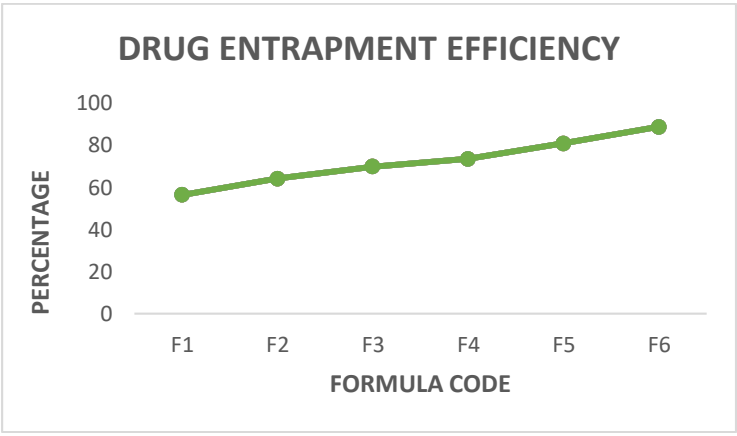
microscopic view of Floating microspheres of pioglitazone

Drug entrapment efficiency:

Percentage drug entrapment efficiency

SR. NO	FORMULA CODE	DRUG ENTRAPMENT EFFICIENCY (%)
1	F1	55.45
2	F2	65.20
3	F3	68.78
4	F4	74.52
5	F5	81.63
6	F6	88.83

The tabular results of microspheres when evaluated through evaluation test like Drug entrapment efficiency was done, it makes crystal clear that F6 has more power to encapsulate the API, as compared to other formula codes. What we can conclude from this result is more the coating on core material, more absorption and swelling occur due to bioadhesive nature of Polymer incorporated in making of these microspheres, more will be the Drug entrapment efficiency. As we know that if more drug is entrapped into a particular dosage form, the chances of showing greater efficacy by that particular dosage form increases drastically.

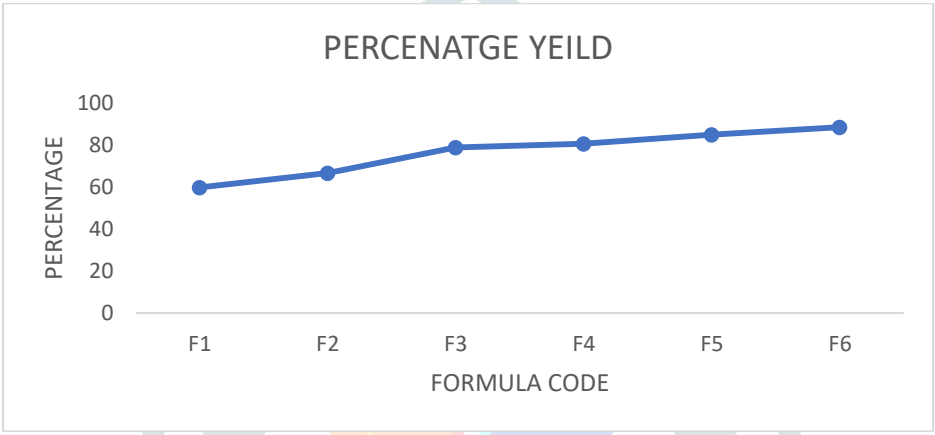


Graphical Representation of Drug entrapment efficiency

Percentage Yield:

SR. NO	FORMULA CODE	PERCENTAGE YIELD
1	F1	46.92
2	F2	54.61
3	F3	62.31
4	F4	70.00
5	F5	77.69
6	F6	85.38

Percentage yeild of various formulations

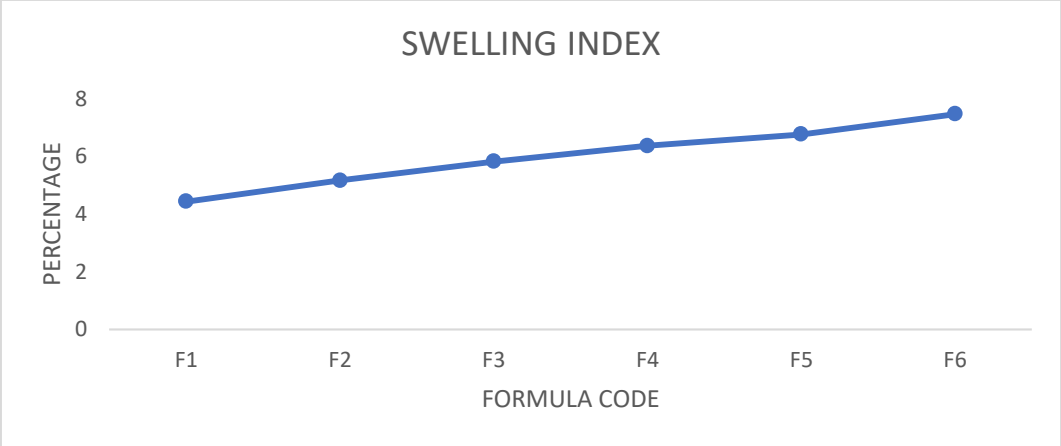


Graphical Representation of Percentage Yield

Swelling Index:

Swelling index is of vital virtue because it is important in deciding which formulation swelled so as to deliver the active drug at the targeted site of action. Upon carrying out tests it was concluded that formula F6 showed better results as compared to all other formulations. It was seen that the swelling capacity is of utmost importance when it comes to floating dosage forms, hence more and more it swells, the maximum it will be effective in delivering the drug at the site targeted to give action.

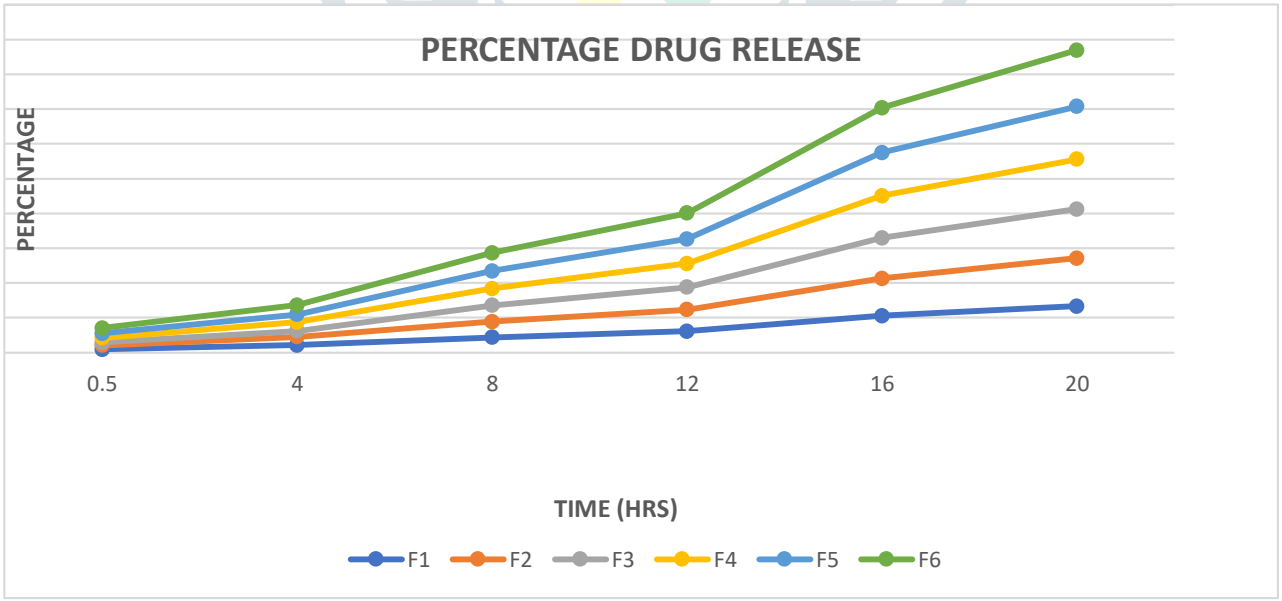
SR. NO	FORMULA CODE	SWELLING INDEX
1	F1	3.62
2	F2	4.24
3	F3	5.36
4	F4	5.73
5	F5	6.76
6	F6	7.58



***In Vitro* studies:**

Data of Invitro tests

TIME (HRS)	F1 %	F2 %	F3 %	F4 %	F5 %	F6 %
0.5	4.42	5.77	5.42	6.29	6.72	7.59
4	9.63	11.58	8.62	12.46	11.33	12.56
8	20.65	21.36	22.44	23.50	24.79	25.21
12	31.24	30.52	31.63	32.89	36.16	38.54
16	52.73	52.53	59.24	62.85	60.82	63.58
20	67.33	68.12	70.85	70.82	75.86	82.02



Graphical Representation of Percentage Drug Release

CONCLUSION

Diabetes is a category of metabolic illnesses defined by a persistently high blood sugar level. It is obvious that

when an illness is chronic in nature, it must be treated with care so that it is completely removed from its roots. Furthermore, we discovered that many of the present medications are ineffective for this aim. Hence,we tried to achieve something differently.

What we finally learnt and concluded from this project was, "Emulsion Solvent Evaporation Technique" is the most suitable and feasible method to prepare microspheres on a lab scale in a hassle-free manner. We tried using various types of polymers and eventually landed with Eudragit S100 and HPMC. An attempt of preparing six different formulations were done with varying degree of Chemicals and solvent in it.

Furthermore, Formula F6 came out as an emerging formulation among all other 6 formulations, giving us a viable and satisfactory readings. As, we were enlightened to know that Formula F6 which was prepared using 100mg of Eudragits S100, 30mg of HPMC happened to the most fit as a dosage form giving promising and satisfactory results. It is also very obvious that, the most vital criteria viz. Floating criteria was very displayed by Formula F6 even after 08 hrs of keeping it under strict vigilance.

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