Design and Development of combine bio adhesive – Floating drug delivery system by using different Polymer

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Abstract-The goal of designing sustained release drug delivery systems of tablets is to reduce the frequency of dosing or to increase the effectiveness of the drug by localization at the site of action, reducing the dose required, or providing controlled drug delivery.1
The oral route is considered as the most promising route of drug delivery. Effective oral drug delivery may depend upon the factor such as gastric emptying process, gastrointestinal transit time of dosage form. Most of the oral dosage forms possess several physiological limitations such as variable gastrointestinal transit, because of variable gastric emptying leading to non-uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach. This lead to incomplete absorption of drug having absorption window especially upper part of small intestine, as once the drug passes down the absorption site the remaining quantity goes down unabsorbed.

Keywords-Ciprofloxacin HCL55-56, HYDROXYPROPYLMETHYLCELLULOSE.

INTRODUCTION

The gastric emptying time of dosage form in humans is affected by several factors because of which wide inter and intra subject variation are observed hence many drugs are well absorbed in the upper part of the gastrointestinal tract such a high variability may lead to non-uniform absorption and make the bioavailability unpredictable. Hence the beneficial delivery system would be one which possesses the ability to control and prolong the gastric emptying time and can deliver the drug in the optimum concentration to the absorption site (i.e. upper part of small intestine)2.

Gastric emptying of dosage form is extremely variable process and ability to prolong and control the emptying time is valuable asset for dosage forms, which reside in the stomach for a long period of time than conventional dosage forms. Several difficulties are faced in designing controlled released system for better absorption and enhancement of bioavailability. Conventional oral dosage forms such as tablets, capsules provide specific drug concentration in circulation without offering any control over drug delivery and also cause great fluctuation in plasma drug level. Although single unit floating dosage forms have been extensively studied, these single unit dosage forms have the disadvantage of release all or nothing emptying process while the multiple unit dosage forms along the Gastrointestinal Tract (GIT) could result in more reproducible drug absorption and reduced risk of local irritation; this gave birth to oral controlled drug delivery and led to development of Gastro-retentive Bioadhesive-Floating tablet3, 4.

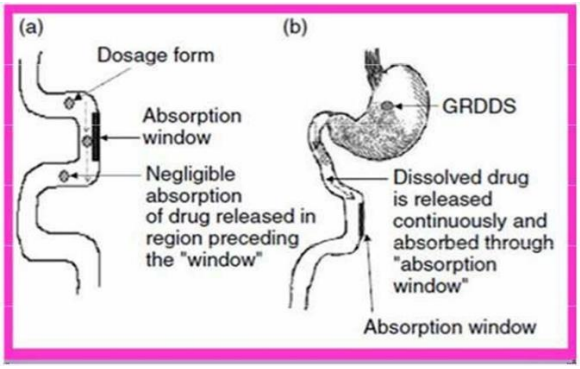


Figure1: Drug absorption in the case of (a) A Conventional dosage form and (b) In GRDDS

Over the three decade, various attempts have been done to remain the dosage form in the stomach as away increasing retention time .High-density system having density 3g/cm3 are retained in the stomach. The only major drawbacks with such system are that it is technically difficult to manufacture them with a large amount of drug (>50%) and to achieve the required density of 2.4-2.8g/cm3. Swelling system are capable of swelling to a size that prevent their passage through the pylorus, the dosage form is retained in the stomach for a longer period of time. Upon coming in contact with gastric fluid, the polymer imbibes water and swells .Bio/mucoadhesive system bind to gastric

epithelial cell surface, or mucin, and extend the Gastro- Retentive time (GRT) by increasing the intimacy and duration of contact between the dosage form and biological membrane.

1.9.1 ADVANTAGES

- Floating system has low bulk density so that they can float on the gastric juice in the stomach. The problem arises when the stomach is completely emptied of gastric fluid.
- In such a situation, there is nothing to float on. But this can be overcome by using bioadhesive – floating drug delivery system.
- In the case of bioadhesive formulation, gastrointestinal motility may be a dislocating force for the dosage form or permanent renewal of the mucus may become an essential limiting factor and specific pH may not be adequate for creating sufficient adhesiveness. But this can be overcome by using bioadhesive- floating drug delivery system.

1.9.2 DISADVANTAGE

- There are certain situation where gastric is not desirable. Aspirin and non- steroidal anti-inflammatory drug known to cause gastric lesions and slow release of such drug in the stomach is unwanted.
- Thus, drug that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastro retentive system.

1.9.3 Drug Suitable For Bioadhesive-Floating Drug Delivery System

i. Drug acting in the stomach
E.g. Antacid, Antibiotics, Antimicrobials
ii. Drugs those are primarily absorbed in the stomach
E.g. Albuterol, Ciprofloxacin, Acyclovir
iii. Drugs those are poorly soluble at an alkaline pH
E.g. Chlordiazepoxide, Cinnarazine, diltiazem
iv. Drug with a narrow window of absorption
E.g. Riboflavin, levodopa
v. Drugs absorbed rapidly form the GI tract
E.g. Amoxicillin
vi. Drugs those degrde in the colon
E.g. Captopril, Ranitidine HCl, Metronidazole, Metformin HCl
vii. Drugs having low solubility at high pH values.
E.g. Diazepam, Furosemide, Verapamil HCl

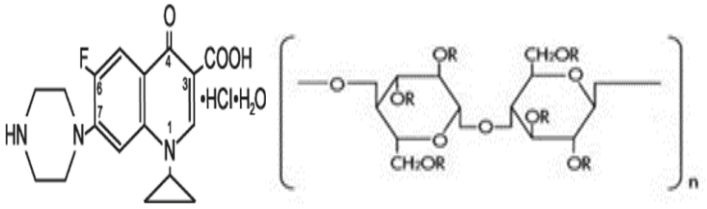
Objectives:

- Objective of present work was to design and develop bioadhesive-floating drug delivery system by using different polymeric systems which got place in the drug delivery research in order of prolonging time of contact in a oral drug administration, so that the drug delivery system can be maintained at an exacting position for prolong duration for local disease treatment and systemic drug bioavailability.
- Also, to fabricate such controlled bioadhesive drug delivery systems which can offer the advantages of better therapeutic efficacy and is easier to comply with than the conventional regimens requiring more frequent dosing and minimize side effects.

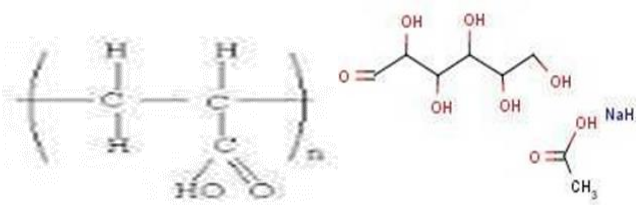
5.Drug and Excipients profile

Structure formula

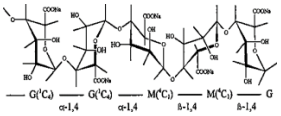
Ciprofloxacin HCL55-56 HYDROXYPROPYLMETHYLCELLULOSE 57



5.3 CARBOPOL [58] SODIUMCARBOXYMETHYLCELLUOSE



5.5 SODIUM ALGINATE [60\]



Experimental work

3.1. Preformulationstudy[65-66]

Preformulation can be defined as investigation of physical and chemical properties of drugs ubstance alone and when combined with excipients. Preformulation studies are the first step in the rational development of dosage form of a drugs ubstance. The objectives of preformulation studies are to develop a portfolio of information about the drugs ubstance, so that this information is useful to develop formulation. Preformulation investigations are designed to identify those physicochemical properties and excipients that may influence the formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of the resulting product. The goals of the program therefore are:

- To establish the necessary physicochemical characteristics of a new drugsubstance.
- Todetermineitskineticreleaserateprofile.
- Toestablishitscompatibilitywithdifferentexcipients.

Hence, a pre formulation study on the obtained sample of drug includes physical test determination and compatibility studies.

3.2Characterizationofciprofloxacinhydrochloride

3.1.1 Organolepticproperties[67]

The drug powder was analysed for colour, odor and taste.

3.1.2 Description[67]

The drug sample (ciprofloxacinhydrochloride) was analysed for physical appearance and powder nature.

3.1.3 Meltingpoint[67]

Melting point determination of ciprofloxacinhydrochloride was done by open capillary method. It is a good first indication of purity of samples in cethepresence of relatively small amount of impurity can be detected by a lowering as well as widening of melting point range.

3.1.4 Solubilityanalysis[67]

A semi quantitative determination of solubility can be made by adding asolute in small incremental amount to fixed volume of solvents, distilled water, phosphate buffer pH 7.4, buffer pH 1.2, 0.1N HCl, methanol, alcohol, isopropylalcohol. After each addition, the system is vigorously shaken and examined usually for any un dissolve particles. When some soluteremains undissolved the total amount added up to that point servers as a goodandrapidestimateofsolid.

3.2MicromeriticcharacterizationofCiprofloxacinhydrochloride

In the Micromeritic properties, Angle of repose, loose bulk density, Tapped bulk densities, Carr's index, Hausner ratio of the pure drug were determined. Methods for the determination of Angle of repose, Loose bulk density, Tapped bulk density, Carr's index, and Hausnerratio.

3.3Spectroscopicstudies [68]

7.4.1UVspectroscopy (Determination of lambdamax)

Stock solution (100µg/ml) of ciprofloxacin hydrochloride was prepared in 0.1M HCl. The solution was kept in a fused silica cuvette 10mm.The UV spectrum was recorded in the range of 254-365nm on Shimazdu UV-visible spectrophotometer (UV-1700) at 1cm, slit width. The same procedure was carried out using0.1 MHCl. It showed max at 275nm using spectrophotometer.

7.5CompatibilitystudiesofCiprofloxacinhydrochloride

andformulationcomponents

The compatibility of drug and polymer under experimental conditions is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymer and excipients under experimental conditions and not affecting the shelf life of productor any other unwanted effects on the formulation.

7.6MicromeriticCharacterizationofDrugandpolymer[71-72]

7.6.1 Evaluation of prepared Powder mixtures

7.6.1.1 Loose bulk Density

The loose bulk density was obtained by dividing the mass of powder by the bulk volume in cm^3. The 10gm sample was carefully introduced into a 25ml graduated cylinder. The volume occupied by the powder was recorded and bulk density then calculated. It was calculated by using equation given below:

$$D_f=M/Vp$$

7.6.1.2 Tapped bulk density:

The tapped bulk density was obtained by dividing the mass of a powder by the tapped volume in cm^3. The 10gm sample was carefully introduced into a 25ml graduated cylinder. The cylinder was dropped at 2-second intervals onto a hard wood surface 100 times from a height of 1 inch.

Compressibility Index and Hausner ratio:

In recent years, the compressibility index and the closely related Hausner ratio have become the simple, fast and popular methods of predicting powder flow characteristics.

Hausner Ratio

Compressibility Index %	Flow property	Hausner Ratio
≤10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
>38	Very, very poor	>1.60

Table No.1: Relationship between Percent compressibility And Flowabilit

Table No. 2: Relationship between angle of (θ) and flow ability

Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair—aid not needed	36–40
Passable—may hang up	41–45
Poor—must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	>66

Formulation and preparation of floating-Bio adhesive tablets of Ciprofloxacin HCl

Sustained release floating- Bio adhesive tablets were prepared by direct compression method. Ciprofloxacin and various concentrations HPMC K- 15M were used as a release retardant polymer. Carbopol -940, Sodium CMC and Sodium alginate were used as bio adhesive polymer. Sodium bicarbonate.

Table no. 3: Formulation Chart of bio adhesive-floating tablet of ciprofloxacin

Batches/Ingredients (mg)	drug	HPMCK-15	Carbopol 940	SodiumCMC	SodiumAlginate	Sodiumbicarbonate	Citricacid	MCC	Total(mg)
F1	500	125	25	-	25	25	25	25	750
F2	500	100	50	-	25	25	25	25	750
F3	500	75	75	-	25	25	25	25	750
F4	500	125	-	25	25	25	25	25	750
F5	500	100	-	50	25	25	25	25	750
F6	500	75	-	75	25	25	25	25	750
F7	500	100	25	25	25	25	25	25	750
F8	500	125	12.5	12.5	25	25	25	25	750
F9	500	150	-	-	25	25	25	25	750

Evaluation of Ciprofloxacin bioadhesive-floating tablets

Weight variation test [65, 66, 71, 72]

Weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average USP weight variation test. The table No4 given below shows the weight variation tolerance for uncoated tablets.

Table No.04: Weight variation tolerance for uncoated tablets

Average weight of Tablet (mg)	Maximum percent deviation allowed
80mg or less	10%
80mg to 250mg	7.5%
More than 250mg	5%

Hardness

The hardness of 3 tablets, from each batch was determined and means hardness was taken into account, which was expressed in kg/cm2.

Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. Tablets were deducted and re-weighed. Compressed tablets should not loose more than 1% of their weight.

Content uniformity

For this at least 30 tablets were randomly selected. Out of 30 tablets, 10 tablets were crushed into fine powder and assayed individually; the tablet should be within 85% to 115% of the labeled claim.

Thickness

The thickness of the tablet was measured using Verniercalliper. Thickness of three tablets from each batch was measured and mean was calculated.

Swelling characteristics of tablet

The extent of swelling was measured in term of percent weight gain by the tablets. The swelling behaviour of formulation was studied. One tablet from each formulation was kept in Petri dish containing for 0.1N HCl 12 hours. At the end of each hour tablet was withdrawn soaked with tissue paper and weighed. Then after every hrs. Swelling index of tablet was calculated using formula.

Determination of floating capacity

In vitro bio adhesion study.

Bio adhesive strengths of the tablets were measured on a modified physical balance (Figure.no.13). The apparatus consist of a modified double beam physical balance in which a right and left pans has been replaced by lighter pans. The left side of the balance was made 5gm heavier than the right side by placing 5gm weight on left side pan

Figure 02: Bio adhesion Test study assembly

Table No.05: Parameters of dissolution study

Speedofrotation	50rpm
No.oftabletstested	6tablets
Temperature	37ºC±0.5ºC
Time	24hours
TestMedium	0.1NHCL
Volumeoftestmedium	900mlineachvesselfor24hrs.
Samplingtime	Eachtwohours

EffectofdrugreleaseinintestinalpHcondition[85,86,and87]

Model fitting [88, 89,90,91,92]

The model fitting for % cumulative release was done using PCP software to find the best fits kinetic equation for the dissolution profile

Kinetics of drug release

In order to understand the mechanism and kinetics of drug release, the results of the in-vitro dissolution study of the optimized batch was fitted with various kinetic equations like.

Zero order (% Release =Kt),

First order (log % Unreleased =Kt),

Higuchi's model (% Release =Kt0.5) and

Pappas Korsmeyer equation (% Release=Ktn)

Stability studies of ciprofloxacin hydrochloride matrix tablets

TableNo.06: Parameters studied on F2, formulations before and after stability study

Parameters	Stabilitystudy			
	Atinitial	After 1month	After2month	After3month
Thickness	5.67±0.008	5.67±0.008	5.67±0.008	5.67±0.008
Hardness	5.3±0.4	5.2±0.4	5.3±0.4	5.3±0.4
Drugcontent	98.31%	98.28%	98.22%	98.15%

TableNo.07:%CumulativePercentdrugreleasedofoptimizedformulationF2,after stability study

Time (Hrs)	%cumulativedrugrelease			
	Atinitial	After 1month	After2month	After3month
0	0	0	0	0
2	15.61	15.61	15.61	15.61

4	22.98	22.58	22.92	22.76
6	32.94	31.94	31.85	32.48
8	47.04	46.04	44.16	46.92
10	52.40	50.87	51.27	52.25
12	61.30	58.37	59.30	60.85
14	64.04	63.21	62.66	63.95
16	73.75	70.87	71.85	72.25
18	78.77	76.15	75.35	74.50
20	87.96	84.36	83.67	86.58
22	94.81	92.32	93.68	93.35
24	98.19	97.45	99.67	97.95

*All the values are represents as Mean±S.D. (standard deviation) (n=3)

Figure.03: Dissolution profile of formulations F2 before and after stability study

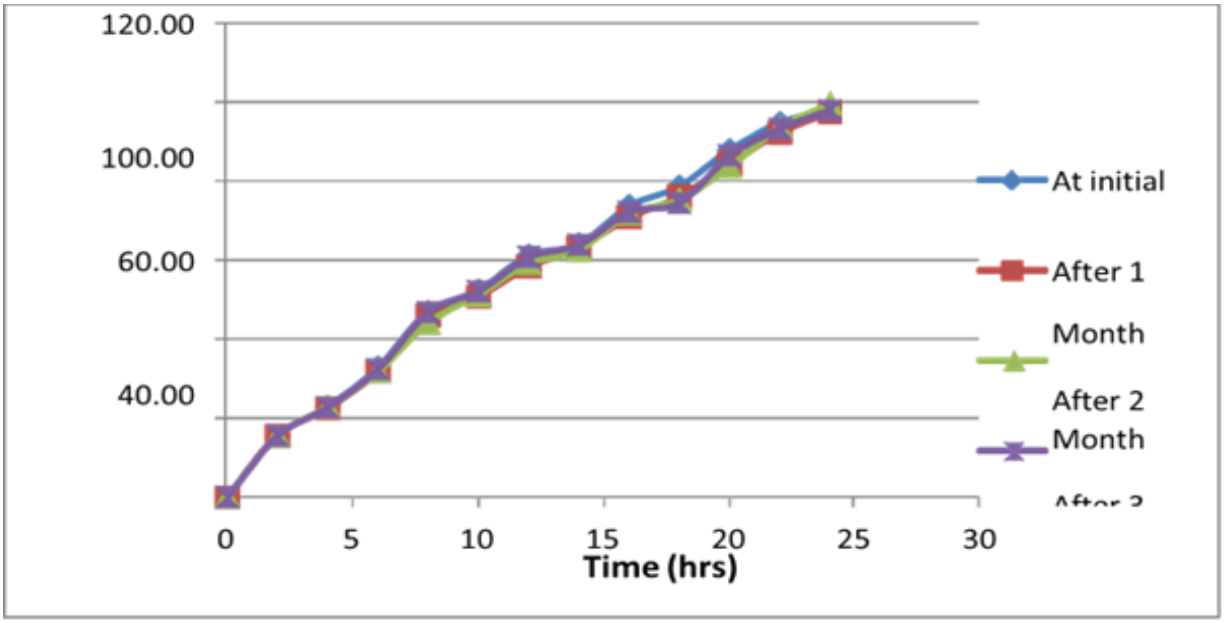


Table no.08: Swelling index of F2 formulation before and after stability study

Time(hr)	Swellingstudy			
	Atinitial	After 1month	After 2month	After3month
1	33.33	31.65	32.12	33.19
2	36.25	32.35	34.57	33.58
4	65.10	62.57	61.79	64.84
6	78.20	74.69	76.15	77.23
8	103.28	100.25	102.89	102.89
10	120.22	118.69	120.12	119.46
12	97.38	96.89	101.21	98.08

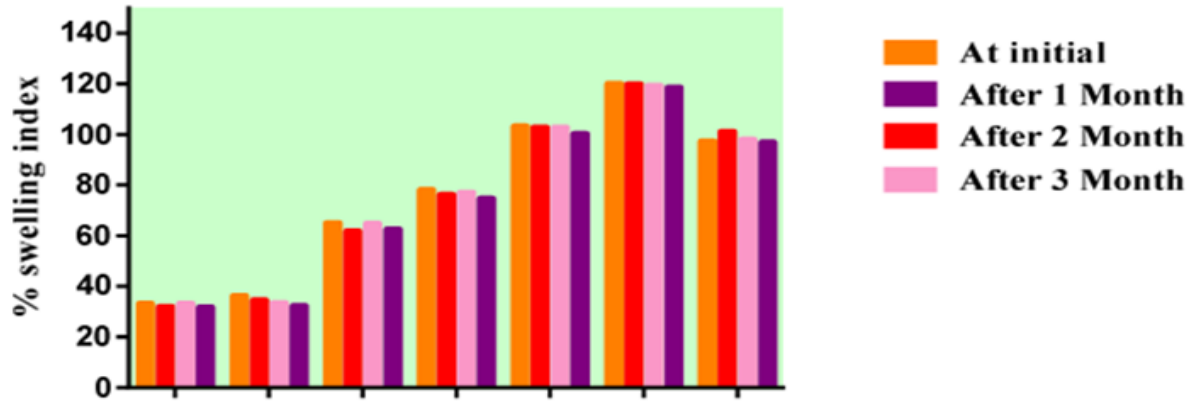


Figure.04:SwellingindexofformulationsF2beforeandafterstability

Table 09: Floating capacity of F2 formulation before and after stability study

Time(hr)	Floatingcapacity	
	Floating lagtime(sec)	Totalfloatingtime
Atinitial	20	Morethan12hr.
After 1 Month	24	Morethan12hr.
After 2 month	21	Morethan12hr.
After 3 month	22	Morethan12hr.

Table10:*Invitro*bioadhesionstudyofF2formulationbeforeandafterstability

Time(hr)	*Invitro*bioadhesionstudy	
	BioadhesiveStrength(gm)	BioadhesiveForce(N)
Atinitial	19.38	0.1935
After 1Month	19.34	0.1932
After 2 month	19.37	0.1931
After 3 month	19.36	0.1934

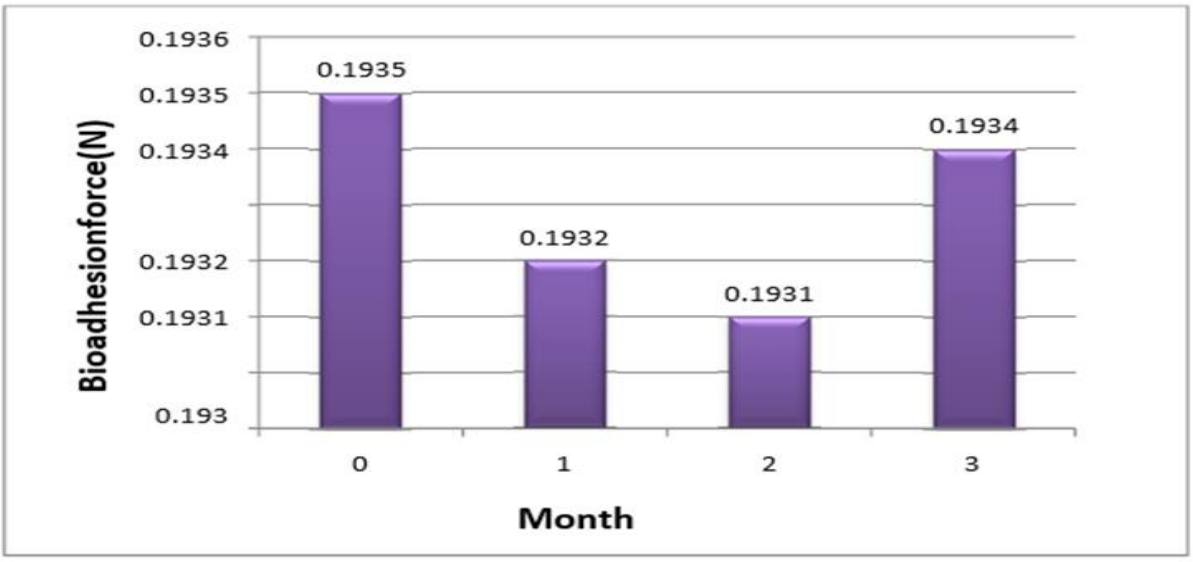


Figure.05: *Invitro* bioadhesion study of formulationsF2beforeandafterstability

Summary and Conclusion

Main challenge to controlled/sustained release drug delivery system is to uphold the drug delivery system at exacting site for extensive time period for local and systemic bioavailability of drug also these system has disadvantage of less gastric retention time, which is a physiological limitation that leads to lower bioavailability of drug. Mostly, for a conventional dosage form the dosing intervals of the drug are much less than the drug half-life leads to numerous limitations.

The remedy for above problems is the development of controlled and targeted drug delivery system of existing drugs which are effective and safe. Therefore bioadhesive-floating dosage form has been selected which remained intact at an exacting site for extensive time period to provide a longer residence time and prolonged release of drug.

Futurescope

It can be used to study the target oriented release of drug in the cure of disease related to stomach.

Development of dosage form by using various bioadhesive polymers.

Development of bioadhesive strength study model.

*Invitro*gastroretentive gamma-scintigraphy study of present work.

Studytheeffectoftabletshapeandsizeonthecharacteristicsofsuchdosageform**.**

*Invitro-invivo*correlationofpresentstudy.

REFERENCES

[1] Lachman L., Lieberman HA, Kanig Joseph L., "The theory and practice of Industrial pharmacy", Verghese publishing house, 3rded, 1990; 346.

[2] Rouge and Buri.p and Doelker.E.E. "Drug absorption site in gastrointestinal tract and dosage form for site specific delivery" Int. J Pharm. 136(1996), 117-139.

[3] Chien Y.W., "controlled an Modulated Release Drug Delivery System ", in Encyclopedia of Pharmaceutical Technology, J. Swarbrick , J.C. Boylan Eds., Marcel Dekker Inc., New York (1990)280-285.

[4] Jain, N.K. "controlled Novel Drug Delivery, Ist Eds., CBS Publishers and Distributors, New Delhi, (2002)236-255.

[5] Arora S, Ali J, Khar RK, "Floating drug delivery system; A review", AAPS Pharm SciTech. (2005)6(3), E72-E390.

[6] Ross and Wilson, "Anatomy and Physiology in heath and illness" 9th Edition, Churchill Livingstone, USA (1996)295-297.

[7] Nikita Dixit: Floating Drug Delivery System. "Journal of current pharmaceutical research"7(1): 6-20. 2011.

[8] Manisha Ware, Sandip Prasad Tiwari, review on "New Insights In to Gastro- Retentive Floating Drug Delivery Systems", World Journal of Pharmacy and Pharmaceutical Sciences. ISSN 2278 – 4357. Volume 3, Issue 1, 252-270.

[9] Shivkumar H G, Vishakante D, Pramodkumar TM. "Floating controlled drug delivery systems for the prolonged gastric residence: a review" Indian J Pharm Educ. (2004) 38(4): 172-179.

[10] Stanley S. Davis. A review: Formulation strategies for absorption window; DDT, February 2005, Vol.10 (4).

[11] NehaNarang, Research On "Floating Drug Delivery System (Fdds)"IJAP, Issn- 0975-7058. Vol 3, Issue 1, 2011.