DEVELOPMENT AND CHARACTERIZATION FUROSEMIDE LOADED MUCOADHESIVE MICROSPHERE

Vikas Sharma[1*], Jiyaul Hak[2], Dr. Mojahid ul Islam, Dr. Prabhakar Vishvakarma[4]

[1*]Research Scholar, Department of Pharmacy, IIMT College of medical sciences, IIMT University Meerut 250001,Uttar Pradesh, India
[2]Department of Pharmacy, IIMT College of medical sciences, IIMT University Meerut 250001, Uttar Pradesh,India
[3]Department of Pharmacy, IIMT College of medical sciences, IIMT University Meerut 250001, Uttar Pradesh, India
[4]Department of Pharmacy, IIMT College of medical sciences, IIMT University Meerut 250001, Uttar Pradesh, India

***Corresponding Author:** Vikas Sharma[1*]
[*]Research Scholar, Department of Pharmacy, IIMT College of medical sciences, IIMT University Meerut 250001, Uttar Pradesh, India

DOI: 10.48047/ecb/2023.12.si5a.0449

1. INTRODUCTION

1.1 Solid dispersion

Solid dispersion can be defined as a dispersion in which drug eutectic mixes are formed with water-soluble carriers by melting of their physical mixtures. The term "solid dispersion" refers to an inert carrier and matrix containing one or more active ingredients that have been dispersed in a solid form using a melt, fusion, solvent, or melts solvent preparation process.

The drug's permeability and oral bioavailability are significantly influenced by its solubility. Some medications' solubility makes it difficult for their formulation to be acceptable for oral administration. The hydrophobic medication and the hydrophilic matrix are used to create the solid products, which are made up of at least two distinct components. The dispersion matrix may have either an amorphous or crystalline shape. The medication may then be dissolved, either in crystalline or amorphous form[1-5].

1.1.2 Advantages

Using solid dispersion technology has various reasons for improvement of solubility of poor water soluble drug. Advantages of solid dispersions are as follows:

1. The drugs porosity to improvement.
2. To dispenser the gaseous and liquid compounds
3. To mask the taste and color of the drug substances.
4. Reduced the particle size of the drug.

1.1.3 Disadvantages

1. The risk of precipitation upon dilution with aqueous media which compound is less soluble.
2. The tolerability and toxicity is related with use of a non physiological pH and extreme pH.

1.1.4 Applications

1. To enhance the drug absorption;
2. To obtain a homogeneous a small amount distribution of drug in solid state;
3. Used for stabilize to unstable drugs and protect against decomposition by processes like photo oxidation hydrolysis, oxidation, etc.
4. To dispense in liquid or gaseous compounds;
5. To formulate a fast release dose in sustained release dosage form with control release;
6. To form a sustained release preparation of soluble drugs by dispersing drug in insoluble carrier or poor soluble;
7. To reduce side effects - (a) the drugs binding ability e.g. the erythrocyte membrane is reduce by making its complex,(b) Damage to stomach mucous membranes by some non-steroidal anti-inflammatory drugs (NSAIDs) can be reduced through administration an inclusion compound.
8. To mask the smell and unpleasant taste of the drug. For example the bed taste of anti-depressant famoxetine to development oral liquid formulations which give bitter taste was greatly suppressed when famoxetine solid complex was formulated aqueous suspension;
9. To convert liquid compounds to solid formulations. Liquid drugs can be manufactured the solid drug formulations like powders, tablets or capsules e.g., unsaturated fatty acids, prostaglandin, clofibrate, essential oils, nitroglycerin, benzaldehyde etc.
10. The poorly soluble drugs solubility are increase the absorption, dissolution rate, and bioavailabilty.
11. The masking of the unpleasant taste, clour and smell of drugs.
12. To improve the drug release from in shampoo, ointment, creams, and gels.
13. It reduces the side effect of the certain drugs and its dosage form. [6-10]

1.1.5 TYPES OF SOLID DISPERSION

1. Eutectic mixtures

Two chemicals that are completely miscible in liquid form but only to a very limited amount in solid form make up a simple eutectic combination. Rapid solidification of two components melts results in the creation of eutectic mixtures, which exhibit full liquid miscibility but minimal solid-solid solution.

2. Solid solutions with discontinuities

In discontinuous solid solutions, the solubility of components in other components is limited. Only solid solutions with a mutual solubility of at least 5% between the two components should use it.

3. Glass suspensions and solutions
The solute dissolves in a glass carrier in this homogenous glassy system. The glass solvent is used to suspend the glass suspension mixture of precipitated particles.

4.Crystalline precipitation of amorphous material
The substance is precipitated to create an amorphous state, comparable to a straightforward eutectic combination.

5. Supplementary solid dispersions
Only when the size of the solute molecules varies by less than 15% is substitution feasible. The solute molecules may either replace the solvent molecules in the crystal lattice or fit into the interstices between the solvent molecules in solid solutions that have crystalline structure.

6. Reliable remedy
In contrast to liquid solutions, solid solutions only include one phase, regardless of the number of components. Particle size of drugs in solid solutions has been lowered. [11-12]

1.1.6 Polymers used in the mucoadhesive microspheres formulation
Mucoadhesive polymers are swellable networks of both water-soluble and water-insoluble types that are connected by cross-linking agents. These polymers provide enough mucus wetting and have the best fluidity, allowing the mucus membrane and polymer to interact and adsorb to one another. Mucin epithelium surfaces attach to mucoadhesive polymers, which are broadly categorised into three groups [13].

1. Stickiness is what gives sticky polymers in water their ability to adhere to mucous membranes.
2. It may be important for polymers to connect by non-specific, non-covalent interactions that are largely electrostatic in nature and include hydrogen and lipophilic bonding.
3. Polymers connect with certain receptor sites.
   Drug delivery may employ three different kinds of polymers.

1.1.7 Traditional non-specific first generation mucoadhesive polymers
First generation mucoadhesive polymers are divided in three type:-
(1) Anionic polymers
(2) Cationic polymers
(3) Non-ionic polymers.

Anionic and cationic polymers have show to exhibit greatest mucoadhesive strength.
Consequently, charged polymeric systems will be examined in more depth.

1.1.8 Novel second-generation mucoadhesive polymers
1. Lectins
2. Thiolated polymers

2. MATERIAL AND METHOD

2.1 Material
The drug Furosemidewas obtained gift sample from Sunpharma (Himanchal Pradesh), Calcium carbonate from S d fine Chem limited, Mumbai, Mannitol from S d fine Chem limited, PEG-400

From S d fine Chem limited, PEG-6000 from S d fine Chem limited, β-cyclodextrin Yarrow Chem products, Mumbai and Sodium alginate from S d fine Chem limited, Mumbai.[14-18]

2.2 Methodology
The microcapsule coating is combined in a volatile solvent that is immiscible with the liquid vehicle phase during this procedure, which is done in a liquid vehicle. A core material dissolves or disperses the microencapsule in the coating polymer solution, and the combination is then agitated with the core material to disperse the microencapsule into a uniform size in the liquid vehicle phase. If necessary, the mixture is heated to help the polymer of the core material dissolve in the polymer solution and shrink away from the core. The formation of matrix-type microcapsules follows the dispersion of the core material in a coated polymer solution.

The development of an emulsion between an immiscible continuous phase and an polymer solution that is either aqueous (o/w) or non-aqueous, as well as a comparison of mucoadhesive microspheres, constitute the solvent evaporation method [19-25].

2.3 Optimization formula for preparation of Solid dispersion

TABLE NO: 1Optimization formula for preparation of Solid dispersion

Gredients formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg
PEG 4000	500 mg	1.0 gm	_	_	_	_	_	_	_	_	_	_
PEG 6000	_	_	500 mg	1.0 gm	_	_	_	_	_	_	_	_
Mannitol	_	_	_	_	250 mg	500 gm	1.0 gm	1.5 gm	_	_	_	_
β-cyclodextrin	_	_	_	_	_	_	_	_	250 mg	500 mg	1.0 gm	1.5 gm

Represents the formulation by using ingredients in different ratio n = 12

3. RESULT AND DISCUSSION

3.1. Preformulation Studies

3.1.1. PHYSICAL EVALUATION: THE DRUG WAS EVALUATED FOR ITS PHYSICAL FORM AND ORGANOLEPTIC PROPERTIES.

ORGANOLEPTIC PROPERTIES AND PHYSICAL FORM OF FUROSEMIDE ARE FOLLOWING

TABLE NO.2:- ORGANOLEPTIC PROPERTIES AND PHYSICAL FORM OF FUROSEMIDE

S. NO.	ORGENOLEPTIC PROPERTIES	
1	DESCRIPTION	FINE CRYSTALLINE POWDER
2	COLOUR	YELLOWISH WHITE COLOUR
3	ODOUR	PUNGENT
4	TASTE	TASTELESS

3.1.2. WAVELENGTH MAXIMUM (ʎmax) OF FUROSEMIDE

THE FUROSEMIDESOLUTION OF (6 µG/ML) WAS PREPARED IN WATER, METHANOL, PHOSPHATE BUFFER 6.8, AND PHOSPHATE BUFFER 7.8 AND THEN SCANNED USING SHIMADZU, DOUBLE BEAM UV-VIS SPECTROPHOTOMETRY 1700). THE SCANNING RANGE WAS BETWEEN 200NM TO 400NM.

Maximum lemda max was obtained **ʎmax 235 nm** [26-32].

3.1.3. Partition coefficient

1. Partition coefficient of Drug in n-Octanol and water

Partition coefficient value ofdrug in n-octanol and water was found to be 1.34.

2. Partition coefficient of Drug in Octanol and pH 6.8 phosphate buffer

Partition coefficient value of drug in phosphate buffer (pH6.8) was found to be 1.41.

3. Partition coefficient of Drug in Octanol and pH 7.4 phosphate buffer

Partition coefficient value of drug in Octanol and phosphate buffer (pH 7.4) was found to be 1.45.

3.1.4. Melting Point

TABLE NO-3:- Melting point of furosemide

S.No.	Melting point (ºC)	Average ± S.D.
1	104.7	104.7 ± 0.5
2	105.3	
3	104.2	

The above experiment result revealed that observed melting point value i.e. 104.7ºC of model API was matched with value given in standard literature. Hence it was used as preliminary identification tool.

3.1.5. Quantitative estimation of drug

3.1.5.1 Praparation of calibration curve of furosemide in different solvent

A. Preparation of calibration curve of furosemide in methanol (λ_{max} 235 nm)

TABLE NO-4:- Calibration curve of Furosemidein methanol

S.no	Concentration(µg/ml)	Absorbance
1	5	0.304
2	10	0.381
3	15	0.459
4	20	0.483
5	25	0.547

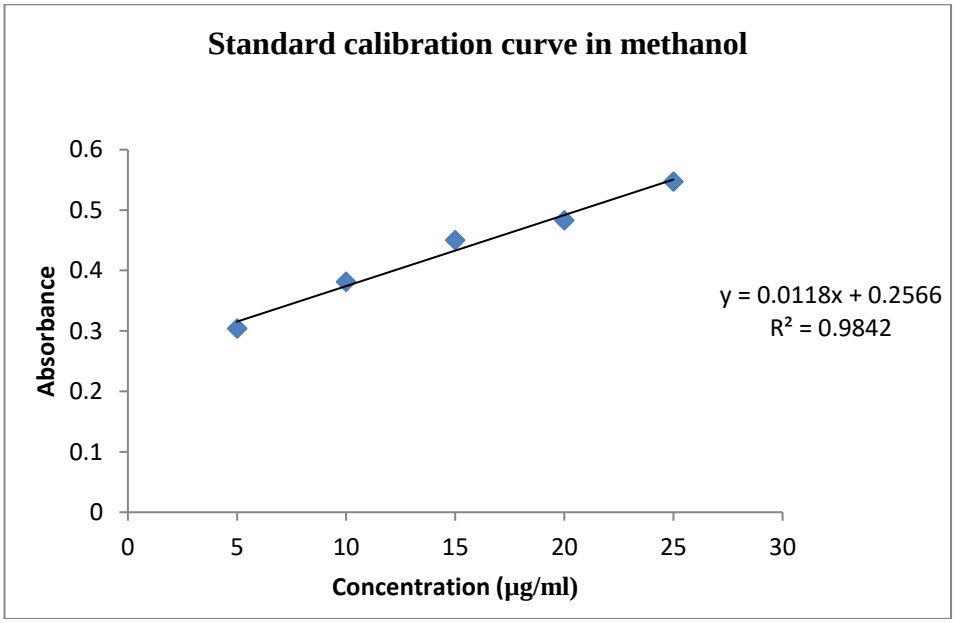

Figure-1:- Calibration curve of furosemide in methanol

B. Preparation of furosemide calibration curve in phosphate buffer pH 6.8 (λ_{max} 235 nm)

TABLE NO: 5- The furosemide calibration curve in phosphate buffer pH 6.8

S. No.	Concentration(µg/ml)	Absorbance
1	5	0.258
2	10	0.372
3	15	0.58
4	20	0.644
5	25	0.779

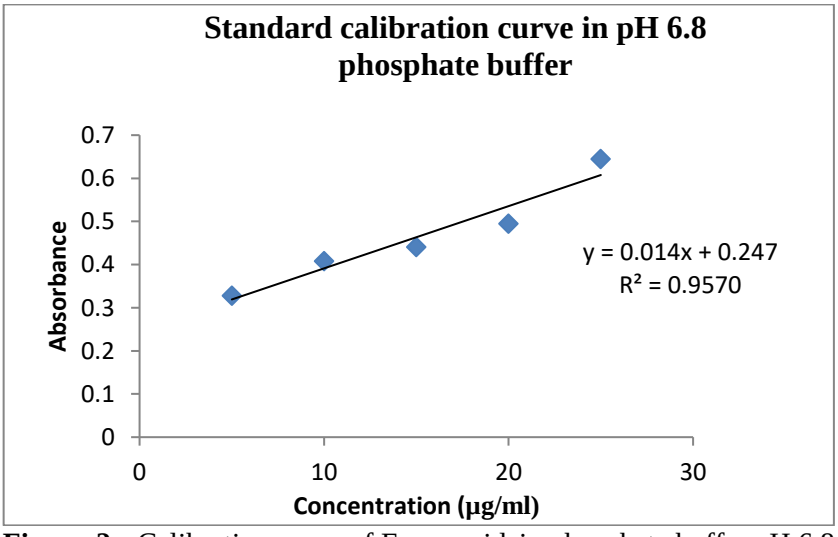

Figure-2:- Calibration curve of Furosemidein phosphate buffer pH 6.8

C. Preparation of Furosemidecalibration curve in 0.1N HCl (λ_{max} 235nm)

TABLE NO-6:- Calibration curve of Furosemidein 0.1N HCl

S.NO.	Concentration (µg/ml)	Absorbance
1	2	0.016
2	4	0.029
3	6	0.041
4	8	0.052
5	10	0.068

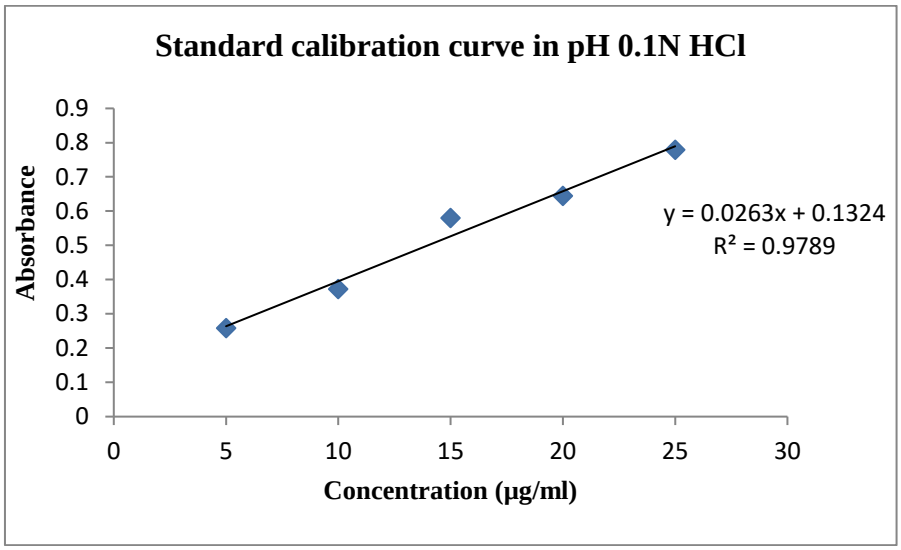

Figure-3:- Calibration curve of Furosemidein 0.1N HCl

D. Preparation of calibration curve of furosemide in phosphate buffer pH- 7.4(λ_{max} 235nm)

TABLE NO:7 - Calibration curve of furosemide in phosphate buffer pH-7.4

S.NO.	Concentration (µg/ml)	Absorbance
1	2	0.024
2	4	0.034
3	6	0.043
4	8	0.054
5	10	0.063

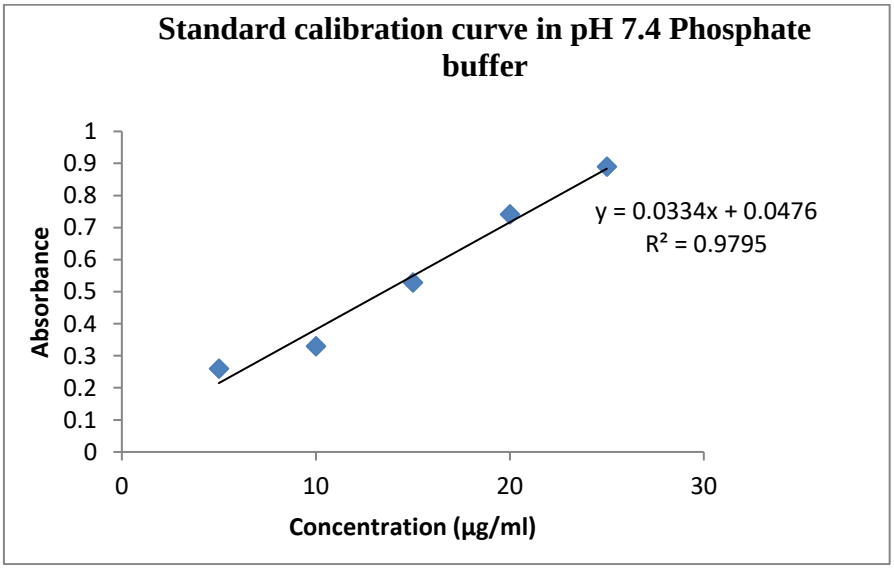

Figure-4:- Calibration curve of Furosemidein phosphate buffer pH-7.4

As per the experimental result all four prepared standard curve having regression value above 0.95, which signify the reproducibility and linearity [33-35]

IR SPECTROSCOPY

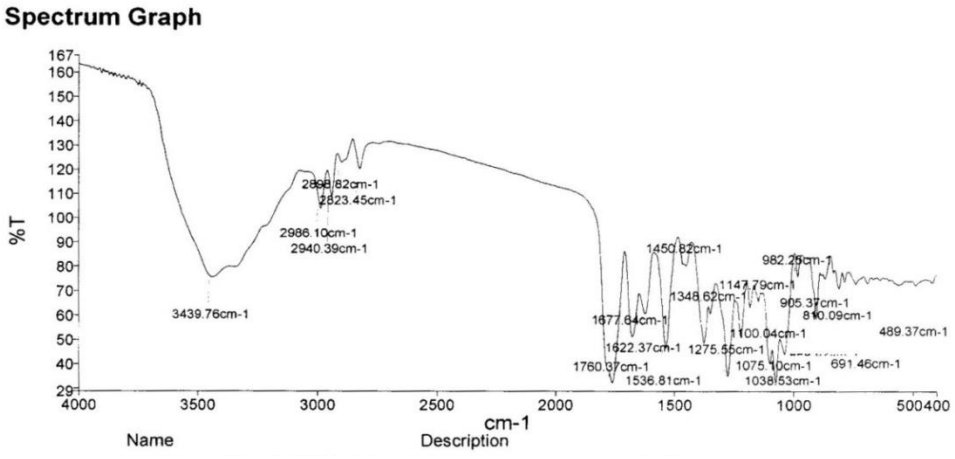

Figure-5:- FTIR of Furosemide

The drug and excipient were taken in 1:1 ratio mixed properly using a poly bag. Now the mixtures were transferred into the glass vials and samples were placed in stability chamber at 40^0C for 21 days.

Through Fourier Transform Infrared Spectroscopy:.

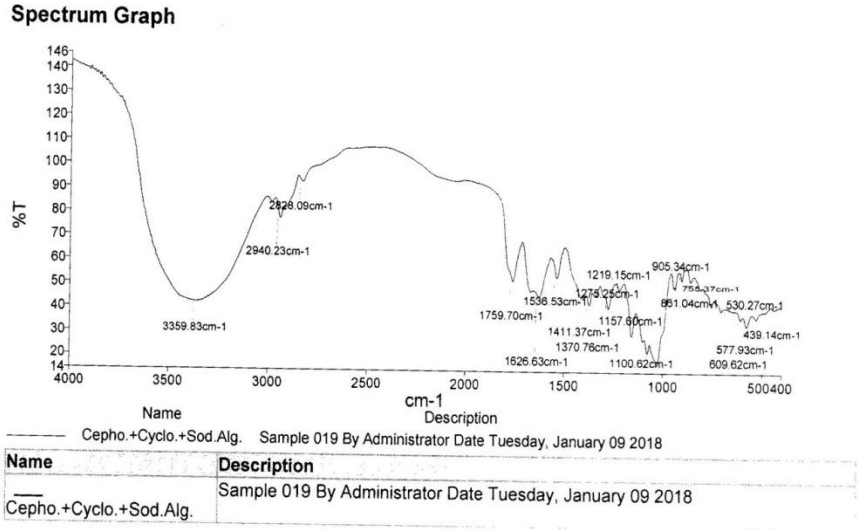

Figure-6:- FTIR of Furosidewith beta-cyclodextrin and sod. alginate polymer

3.1.6 Evaluation of solid dispersion

3.1.6.1 Percentase Practical yield

% practical yield of solid dispersion using defferent polymer

TABLE NO: 8- % practical yield of furosemide solid dispersion using different polymer ratio

Formulation	% practical yield
F1	87
F2	79.1
F3	80.3
F4	72.4
F5	82.6
F6	85.6
F7	88.5
F8	79.7
F9	86.5
F10	90.7
F11	89.7
F12	83.4

The twelve formulations are prepared using different polymer ratio were evaluated. The percentase practical yield range for all the formulation was founded to be 79.1–90.7. The formulation F10 which contain1:1 drug polymer ratio showed higher % practical yield 90.7 % [36-40].

3.1.6.2 Drug content

Drug content of Furosemidesolid dispersion using differentpolymer ratio

TABLE NO:9 - Drug content of Furosemidesolid dispersion using different polymer ratio

Formulation	Drug content
F1	86.6
F2	84.5
F3	78.7
F4	82.3
F5	74.8
F6	74.7
F7	75.3
F8	78.7
F9	77.7
F10	89.4
F11	87.2
F12	85.6

The twelve formulations are prepared using different polymer ratio were evaluated. The drug content range for all the formulation was founded to be 74.7-89.4. The formulation F10 which contain 1:1 drug polymer ratio showed higher drug content 89.4 %.

3.1.7 In-vitro dissolution

In-vitro dissolution of solid dispersion using defferent polymer

TABLE NO:10- In-vitro dissolution of solid dispersion using PEG 4000 & 6000

Time (min)	Percentage drug relase of different ratio of PEG solid dispersion			
	furosemide+ PEG- 4000		Furosemide + PEG-6000	
	F_1 (1:1)	F_2 (1:2)	F_3 (1:1)	F_4 (1:2)
0	0	0	0	0
10	27.5	28.2	11.8	10.45
15	38.9	41.3	26.75	16.75
30	41.5	53.4	36.9	24.7
45	56.7	64.4	40.1	32.9

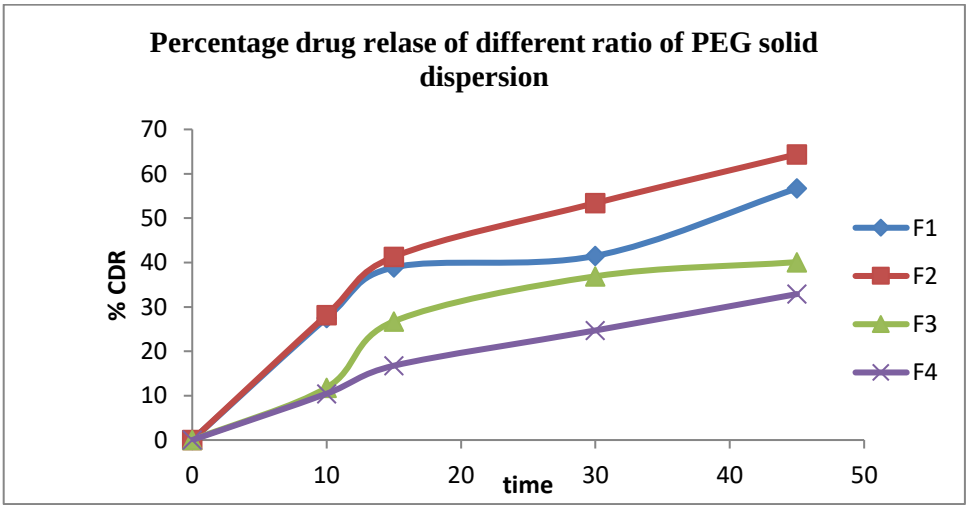

Figure: 7 percentage drug release

1.8 Comparative dissolution profile of furosemide solid dispersion with different polymer and pure drug

TABLE NO:11- Comparative dissolution profile of furosemide solid dispersion with different polymer and pure drug

Time(min)	Percentage drug relase of different solid dispersion formulation and pure drug				
	Drug	F_2 (1:2)	F_3 (1:1)	F_7 (1:1.5)	F_{10} (1:1)
0	0	0	0	0	0
10	10.12	28.2	11.8	27.5	53.2
15	14.34	41.3	26.75	42.1	61.3
30	21.82	53.4	36.9	47.9	74.4
45	29.08	64.4	40.1	54.5	89.4

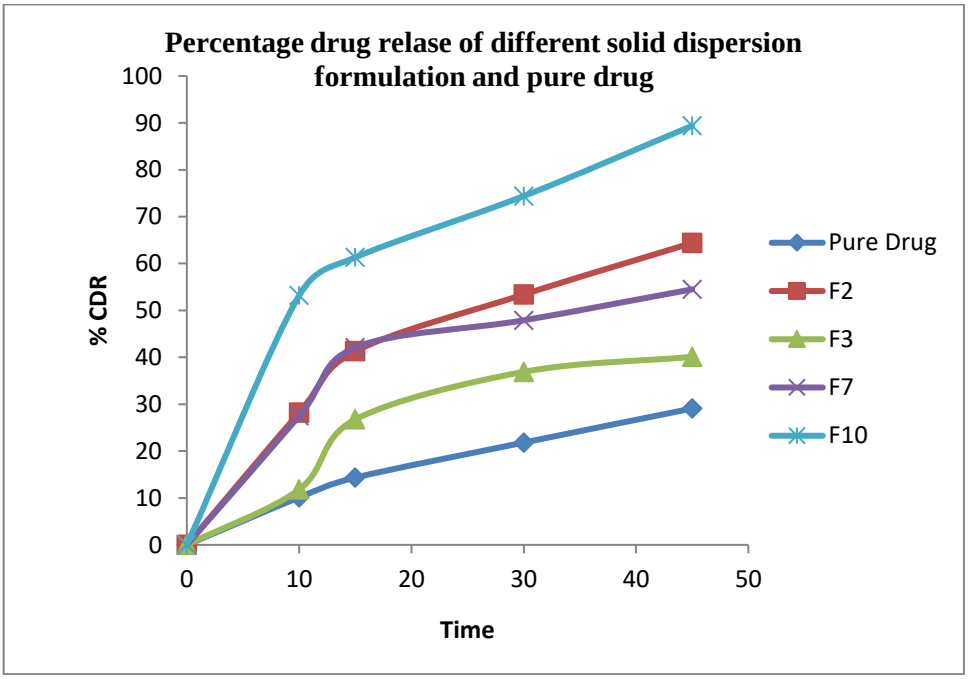

Figure -8:- Comparative dissolution profile of furosemide solid dispersion with different polymer and pure drug

The five formulations are prepared using different polymer ratio and pure drug were evaluated. The formulation F10 which contain 1:1 drug polymer ratio showed higher % CDR as showed in fig. 8.9.

3.1.9 Evaluation of Microsphere

All the prepared mucoadhesive microspheres were evaluated by prelimanary steps such as visual apperance and drug content.

3.1.9.1% Practical yield

% practical yield of defferent ratio sodium alginate microsphere [41-43].

TABLE NO.12:- % practical yield of defferent ratio of sodium alginate microsphere

Formulation	% practical yield
MS1	85.4
MS2	90.4
MS3	88.3
MS4	85.3

The four formulations are prepared using different sodium alginate ratio were evaluated. The percentase practical yield range for all the formulation was founded to be 85.3–90.4. The formulation MS2 which contain1:1 drug polymer ratio showed highest % practical yield 90.4 %.

3.1.9.2 Drug content

Drug content of different ratio sodium alginate microsphere

TABLE NO: 13- Drug content of different ratio sodium alginate microsphere

Formulation	Drug content
MS1	74.3
MS2	86.3
MS3	83.5
MS4	79.0

The four formulations are prepared using different polymer ratio were evaluated. The drug content range for all the formulation was founded to be

74.3–86.3. The formulation MS2 which contain1:1 drug polymer ratio showed highest % practical yield 90.7 %.

3.1.10 Entrapment efficacy

Entrapment efficacy of different ratio sodium alginate microsphere

TABLE NO 14:-Entrapment efficacy of different ratio sodium alginate microsphere

Formulation	Entrapment efficacy
MS1	72.5
MS2	86.3
MS3	87.5
MS4	89.0

The four formulations are prepared using different polymer ratio were evaluated. The entrapment efficacy range for all the formulation was founded to be 72.5-89.0. The formulation MS4 which contain1:2 drug polymer ratio showed higher entrapment efficacy 89.0 %[44-46].

3.1.11. Mucoadhesive test

Mucoadhesive test of defferent ratio sodium alginate microsphere

TABLE NO:15 - Mucoadhesive test of different ratio sodium alginate microsphere

Formulation	Mucoadhesion
MS1	74.3
MS2	86.3
MS3	88.5
MS4	92.3

The four formulations are prepared using different polymer ratio were evaluated. The mucoadhesion for all the formulation were founded to be 73.5-92.3. The formulation MS4 which contain1:2 drug polymer ratio showed higher mucoadhesion 92.3 %.

3.1.12. Swelling index

Swelling index ofdefferent ratio sodium alginate microsphere

TABLE NO.16:- Swelling index of different ratio sodium alginate microsphere

Formulation	Swelling index
MS1	78.3
MS2	86.3
MS3	83.5
MS4	84.0

The four formulations are prepared using different polymer ratio were evaluated. The swelling index range for all the formulation was founded to be 72.5-89.0. The formulation MS4 which contain1:2 drug polymer ratio showed higher swelling index 89.0 %.

3.1.13. In-Vitro Release Studies

The solid dispersion having drug: polymer ratio 1:1 was obtain as base formulation away all 12 solid dispersion formulation. The optimized solid dispersion formulation (F10) was incorporated in microsphere and make 4 different formulation prepared. All formulation are evaluated at pH 1.2 HCl but no release of drug cause of enteric coating and then evaluated at pH 6.8 phosphate buffer. MS2 formulation is best formulation which containing 1gm solid dispersion and showed miximum drug release from till formulation as show in fig. 8.10

TABLE NO.17- Percentage cumulative release of different of Furosemidemicroshpere formulations in phosphate buffer (pH 6.8)

Time interval (hrs)	Percentage drug relase of different formulation 8 hrs			
	MS_1	MS_2	MS_3	MS_4
0	0	0	0	0
0.5	37.42	42.73	39.04	40.12
1	43.67	47.55	44.40	46.67
2	47.75	52.52	50.51	51.34
3	51.18	59.44	56.10	55.11
4	55.74	66.58	65.07	59.26
5	60.45	74.46	71.97	64.08
6	67.93	82.52	77.48	68.31
7	72.45	93.75	84.12	70.15
8	82.86	97.89	86.10	72.02

The four formulations are prepared using different polymer ratio were evaluated. The formulation MS2 which contain 1:1 drug polymer ratio showed higher % CDR as showed in fig. 8.10.

3.1.14. Scanning Electron Microscopy (SEM):- The microspheres were founded smooth surface and the size less than10µm by SEM

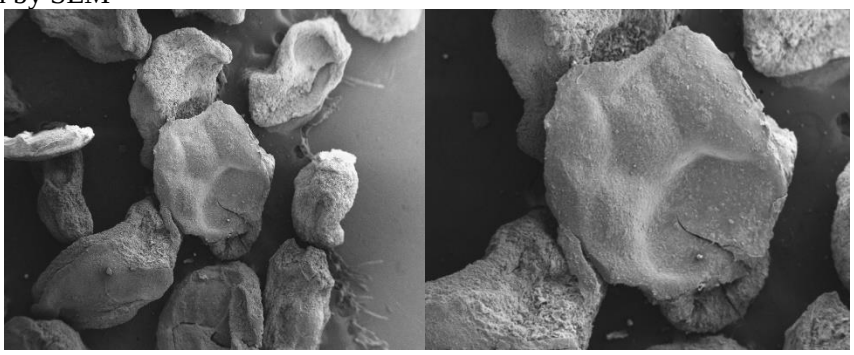

Figure 9:-SEM of Furosemidemicrosphere

3.1.15 Release kinetics study of Optimized formulation (MS_2)

The release kinetic study of the optimized formulation depicts that the best fit model for the optimized formulation is Hixon-crowel with n=0.3013 and the mechanism of release by the formulation follows Higuchi matrix pattern.

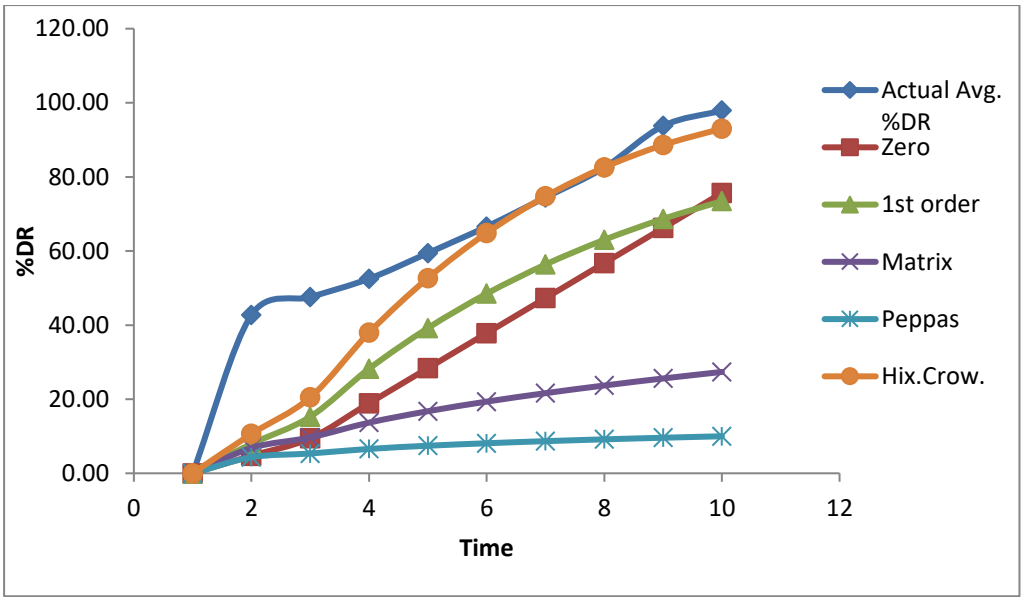

Figure no.10 Release kinetics study of Optimized formulation (MS_2)

TABLENO. 18 Release kinetics study of Optimized formulation (MS_2)

Model Fitting	**R^2**	**K**
Zero order	0.8570	9.4576
1st order	0.8594	-0.3819
Higuchi Matrix	0.9116	9.6729
Peppas	0.9152	5.3417
Hix.Crow.	0.9290	0.0736

Parameters for Korsmeyer-Peppas Equation	
n =	0.3013
k =	5.3417
Best fit model=	Hixon-Crowell
Mechanism of release	
Fickian Diffusion (Higuchi Matrix)	

3.1.16 Accelerated Stability Studies

According to ICH guideline, the accelerated stability studies were carried for prepared gelling system. All these formulation was to analyzed for visual appearance, size, and drug content remaining. Three month of stability study reveal

that there was no chnge in visual appearance and size. All these formulation are showed slight drug content but it was in acceptable limits.

TABLENO: 20 The Formulation's Stability Studies at room temp (pH-6.8)

S.No	Number of day	Percentage Drug Remaining			
		MS1	MS2	MS3	MS4
1	0	98.59	98.95	98.98	98.97
2	15	58.52	98.91	98.85	98.87
3	30	98.51	98.82	98.72	98.75
4	45	98.46	98.75	98.62	98.65
5	60	98.35	98.68	98.53	98.52
6	75	98.08	98.58	98.41	98.43
7	90	98.06	98.51	98.35	98.27
8	105	98.05	98.46	98.24	98.24
9	120	98.03	98.38	98.18	98.19

Conclusion

The objective of the present study was to improve solubility and hence dissolution behavior of poorly soluble drug, Furosemide, by formulating solid dispersions using PEG-4000, PEG-6000, mannitol and β-cyclodextrin. Solvent evaporation method was used for the formulation of solid dispersions and was found satisfactory as it produced good product with high drug content and markedly enhanced drug aqueous solubility. The optimized solid dispersion formulation was then incorporated into mucoadhesive microspheres formulated by ionic gelation method. These microspheres were coated by enteric coating polymer to protect the formulation from the highly acidic environment in the stomach. So formed mucoadhesive microspheres of Furosemide showed enhanced drug release profile and exhibited delayed and sustained release of the drug. From the above study it can be concluded that solid dispersion of the drug enhances its solubility and mucoadhesion of the microspheres leads to sustained delivery of the drug leading to increased therapeutic efficacy and reduced dosage frequency, ultimately making the product patient compliance [47-50].

References-

1. Kora Pattabhi Rama and Yarraguntla Rao 1984. Pharmacokinetic basis for drug treatment. Raven Press, New York. 220-230
2. G.Harish, S.Duraivel, B. Pragathi Kumar 1990. Pharmacokinetics of Furosemide in plasma and skin blister fluid following oral dosing of Furosemide. Antimicrob. Agents Chemother. 34:1094-1099.
3. Borner, K., H. Hartwig, H. Lode, and N. Saathoff. 1990. Liquid chromatographic determination of FUROSEMIDEin human serum and urine. Frensenius' J. Anal. Chem. 337:124.
4. Hemlata Kaurav, S. L. HariKumar and Amanpreet 1988. In vitro activity of an oral iminomethoxy aminothiazolyl cephalosporin, R-3746. Antimicrob. Agents Chemother. 32:671-677.
5. Deppermann, K. M., H. Lode, G. Hoffken, G. Tschink, C. Katz, and P. Koeppe. 1989. Influence of ranitidine, pirenzepine, and aluminium magnesium hydroxide on the bioavailability of various antibiotics, including amoxicillin, cephalexin, doxycycline,and amoxicillin-clavulanic acid. Antimicrob. Agents Chemother. 33:1901-1907.
6. Fass, R. J., and V. L. Helsel. 1988. In vitro activity of U-76.252 (CS-807), a new oral cephalosporin. Antimicrob. Agents Chemother. 32:1082-1085.
7. S.C. Arora, P.K. Sharma, E. Nakayama, H. Nakao, et al. 1987. Studies on orally active cephalosporin esters. J. Antibiot. 40:370-384.
8. Ginsburg, C. M., G. H. McCracken, Jr., M. Petruska, and K. Olson. 1985. Pharmacokinetics and bactericidal activity of cefuroxime axetil. Antimicrob. Agents Chemother. 28:504-507.
9. Shanthi Priya CH, J. H. Wilton, D. J. Thomas, R. W. Schultz, M. E. Lebsack, and A. W. Kinkel. 1989. Inhibition of enoxacin absorption by antacids or ranitidine. Antimicrob. Agents Chemother. 33:615-617.
10. K R Bobe, C R Subrahmanya, Sarasija Suresh, Ranjith Anishetty, Shivani Puri

1983. The pharmacology of cephalexin. Postgrad. Med. J. 59:16-27.
11. Hughes, G. S., D. L. Heald, K. B. Barker, R. K. Patel, C. R. Spillers, K. C. Watts, et al. 1989. The effects of gastric pH and food on the pharmacokinetics of a new oral cephalosporin, FUROSEMIDE proxetil. Clin. Pharmacol. Ther. 6:674-685.
12. Jones, R. N., and A. L. Barry. 1988. Antimicrobial activity and disk diffusion susceptibility testing of U-76,253A (R-3746), the active metabolite of the new cephalosporin ester, U-76,252 (CS-807). Antimicrob. Agents Chemother. 32:443-449.
13. Nirav Patel, Narendra Chotai and J. A. Washington. 1988. Antibacterial activities of cefpodoxime, cefixime, and ceftriaxone. Antimicrob. Agents Chemother. 32:1896-1898.
14. Kobayashi, S., K. Oguch, E. Uchida, et al. 1988. Phase 1 study on CS-807. Chemotherapy (Tokyo) 36:200-213.
15. Sameer H. Lakade, Mangesh R. Bhalekar and C.-M. Hamann. 1978. REVOL-non-linear regression based on the strategy of evolution. EDV Med. Biol. 2:112-117.
16. Langtry, H. D., S. M. Grant, and K. L. Goa. 1989. Famotidine. An updated review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in peptic ulcer disease and other allied diseases. Drugs 38:551-590.
17. Peck, C. C., L. B. Sheiner, and A. I. Nichols. 1984. The problem of choosing weights in nonlinear regression analysis of pharmacokinetic data. Drug Metab. Rev. 15:133-148.
18. Schwarz, G. 1978. Estimating the dimension of a model. Ann. Stat. 6:461-464.
19. Sommers, D. E. K., M. Van Wyk, and J. Moncrieff. 1984. Influence of food and reduced gastric acidity on the bioavailability of bacampicillin and cefuroxime axetil. Br. J. Clin. Pharmacol. 18:535-539.
20. Uchida, E., K. Oguchi, M. Hisaoka, S. Kobayashi, K. Kai, and H. Yasuhara. 1988. Effects of ranitidine, metoclopramide, and anisotropine methylbromide on the availability of furosemide (CS-807) in Japanese healthy subjects. Jpn. J. Clin. Pharmacol. Ther. 19:573-579.
21. Utsui, Y., M. Inoue, and S. Mitsuhashi. 1987. In vitro and in vivo antibacterial activities of CS-807, a new oral cephalosporin. Antimicrob. Agents Chemother. 31:1085-1092.
22. Merck and Co. 1988. Drug delivery device which can be retained in the stomach for a controlled period of time. US 4735804.
23. Merck and Co. 1988. Drug Delivery Device Which Can Be Retained In The Stomach For A Controlled Period Of Time - US 4758436.
24. Merck and Co. 1988. Drug delivery device which can be retained in the stomach for a controlled period of time. US 4767627.
25. Miyazaki ,Y., Yakou, S., Takayama, K. 2008. Comparison of gastroretentive microspheres and sustained-release preparations using theophylline pharmacokinetics. J. Pharm.Pharmacol. 60(6), 693–698.
26. Moes, A.J. 2003. Gastric retention systems for oral drug delivery. Business Briefing: Pharmatech. 157-59.
27. Hamamura T, Terashima H, Ohtani T (1995c). Decrease in dissolution of FUROSEMIDEtablets by gel formation and its improvement. Yakuzaigaku. 55, 175–182.
28. Hareesh Dara, Narasimha Reddy Yellu (2015). Formulation of Time Dependent Controlled Release Tablet of Nimodipine and its Evaluation using Linear Regression Analysis. Journal ofPharma Research. 4(1), 1-8.
29. Hughes GS, Heald DL, Barker KB (1989). The effects of gastric pH and food on the pharmacokinetics of a new oral cephalosporin, FUROSEMIDEproxetil. Clin. Pharmacol. Ther. 46,674–85.
30. Hwang SJ, Park H, Park K (1998). Gastric retentive drug-delivery systems. Crit. Rev.Ther.Drug Carr. Syst. 15, 243-284.31. Abdul BA, Lila KN (2011). Fabrication and in vitro evaluation of

floating matrix tablet of nicorandil using factorial design. J Pharm Res. 4(6), 1950-4.
31. Akiyama Y, Nagahara N, Kashihara T, Hirai S, Toguchi H (1995). In vitro and in vivo evaluation of mucoadhesive microspheres prepared Copyright © 2016 Seirra Journals, gastrointestinal tract using polyglycerol esters of fatty acids and a poly (acrylic acid) derivative. Pharm. Res. 12, 397-405.
32. Borin T (1991). A review of the pharmacokinetics of FUROSEMIDEproxetil. Drugs. 42, 13–21.
33. B Ramu, N. Ramakrishna, Meruva Sathish, D. Anoosha (2015). Formulation of tellmisartan Hcl Fast Disintegrating Tablets by Sublimation Technique. International Journal of Pharm Tech Research. 8(3), 330-339.
34. Crauste-Manciet S, Huneau JF, Decroix MO, Tome D, Chaumeil JC (1997). FUROSEMIDEesterase activity in rabbit small intestine: role in the partial FUROSEMIDEabsorption. Int. J. Pharm. 149, 241–249.
35. Deshpande AA, Rhodes CT, Shah NH, Malick AW (1996). Controlled-release drug deliverysystems for prolonged gastric residence: an overview. Drug Dev. Ind. Pharm. 22, 531-539.
36. Fix JA, Cargill R, Engle K (1993). Controlled gastric emptying: part3. Gastric residence time of a nondisintegrating geometric shape in human volunteers. Pharm. Res. 10, 1087-1089.
37. Groning R, Berntgen M, Georgarakis M (1998). Acyclovir serum concentrations followingperoral administration of magnetic depot tablets and the influence of extracorporeal magnets to control gastrointestinal transit. Eur. J. Pharm. Biopharm. 46, 285-291.
38. Hamamura T, Kusai A, Nishimura K (1995a). Gel formation of Furosemide. S.T.P. Pharm. Sci. 5, 324–331.
39. Hamamura T, Ohtani T, Kusai A, Nishimura K (1995b). Unusual dissolution behavior ofFurosemide proxetil: effect of pH and ionic factors. S.T.P. Pharm. Sci. 5:332–338.
40. J.Vandervoot, A.Ludwig, Biocompatible stabilizers in the preparation of PLGA nanoparticles, a factorial designstudy, International journal of pharmaceutics 2002, 77-92.
41. T.Vetrichelvan and I.Sowkar Baig, Preparation and in vitro characterization of slow release Abacavir sulfate nanoparticles in aliginate, International journals of biological pharmaceutical research 2011, 144-155.
42. N.jawahar, Preparation and characterization of PLGA-nanoparticles containing an anti-hypertensive agent, International journals of pharma tech research 2009, 1-19.
43. Atul Gaikwad, Formulation and invitro characterization of Olymethacrylic acid nanoparticles containing frusemide, International journals of pharm tech research 2010, 1,300-304.
44. S.Tamizharsi, Formulation and evaluation of lamivudine loaded polymethecrylic acid nanoparticles, International journals of pharm tech research 2009 3,411-415.
45. Sergio.A, Design and characterization of ibuprofen loaded nanoparticles, European journals of pharmaceutics sciences 2005, 125-188.
46. Arvind gulbak, Colon specific delivery of Mesalazine using BIO-compatible polymeric nano-particles2012, 63-72.
47. Rakesh Kumar Sharma, Navneet Sharma, Sudha Rana, Hosakote G. Shivkumar Solid Lipid Nanoparticles as a carrier of Metformin for Transdermal Delivery2013, 69-99.
48. Waree Tiyaboochai, Formulation and evaluation of nanoparticles containing flutamide, International journals of chemistry tech research 2009, 4, 1331-1334.
49. Amolkumar lokhande, satyendra mishra, ravindra kulkarni, jitendra naik* formulation and evaluation of glipizide loaded nanoparticles, Department of Pharmaceutical Technology,University Institute of Chemical Technology, journals of carbohydrate polymers, 2010,833-838.