Research Article

Solubility Enhancement, Formulation and Evaluation of Furosemide Stomach Specific Mucoadhesive Tablet

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ABSTRACT

In the present investigation an attempt was made to enhance the solubility of poorly soluble diuretic furosemide by two methods solid dispersion and complexation, solid dispersions of furosemide with PEG 4000 as a carrier enhanced the solubility more profoundly than complexation method. The selected best formula FSd2 (1:3 furosemide/PEG 4000) subjected to different evaluations including analytical technique like differential scanning caloremitry, powder x-ray diffraction and to dissolution test to prove the change of drug particle from crystal to amorphous form in solid dispersion. The best formula of solid dispersion with different polymers such as HPMC K4M and carpabol 930 p as a single polymer and in combination with different ratios was compressed into stomach specific mucoadhesive sustained release tablets by direct compression method. These tablets enhance absorption of the drug and improve its bioavailability by their gastric retention in stomach. The prepared tablets were evaluated by different parameters such as thickness, hardness, friability, weight variation, content uniformity, swelling index, mucoadhesive strength and *in-vitro* drug release. The results revealed that F2 which contain HPMC K4M as single polymer was chosen as selected mucoadhesive tablet in accordance to *in-vitro* drug release (96%) for 5 hrs, swelling index (40%) and mucoadhesive strength (15.6 gm), the results of *EX-Vivo* gastric retention time study indicated that the selected mucoadhesive tablet remained adhered to the stomach mucosa for 7.10 hr.

Keywords: furosemide, solid dispersion, complexation, gastro retentive, stomach specific mucoadhesive tablet, HPMC K4M.

INTRODUCTION

Oral bioavailability of a drug can be determined by its solubility and/or dissolution rate, and dissolution may be the rate limiting step for appearance of medicinal effect, therefore attempts to increase the dissolution of drug with limited water solubility is desired.[1]

Furosemide is a potent high ceiling (loop) diuretic, mainly used in treatment of hypertension, the drug has been classified as class IV drug as per biopharmaceutical classification, having low solubility and permeability. One of the major causes of low oral bioavailability of furosemide is solubility.[2] The elimination half-life is relatively short (0.5-2hr). Absorption of furosemide after oral use is erratic and subjected to large inter-and intra-individual variation; the bioavailability in healthy persons is approximately from 50% to 70%.[3]

Although Furosemide has very good permeability from the stomach and upper GI tract region but the bioavailability is low and due to poor solubility in gastric fluid.

Though it has good solubility in the intestinal fluid but due to poor permeability through intestinal region makes its absorption very small.[4]

From the biopharmaceutical considerations characteristics, it is desirable to retain furosemide in the stomach in a soluble form; thereby achieving a higher permeability in the stomach and upper GI tract region. Several approaches have been suggested to increase GI transit time, the controlled gastric retention of solid dosage forms may be achieved by different mechanisms such as flotation, sedimentation, expansion, modified shape systems and mucoadhesion/bioadhesion.[5]

For mucoadhesive/bioadhesive drug delivery purpose, the term bioadhesion implies attachment of a drug carrier system to a specific biological location. The biological surface can be epithelial tissue. If adhesive attachment is to a mucus coat, the phenomenon is referred to as mucoadhesion. After oral administration, such a stomach-specific mucoadhesive solid dosage form would be retained in the stomach and release the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the stomach and upper gastrointestinal tract.[6]

The aim of the study is to enhance the solubility of furosemide by two different methods, selecting the best method and formulation and then incorporate it into stomach specific mucoadhesive tablet dosage form, maintaining controlled release of the drug for 5 hrs, thus improving furosemide absorption and bioavailability.

MATERIALS AND METHODS

Materials

Furosemide kindly supplied from (Samara drug industry, Iraq), ß-Cyclodextrin supplied from (Himedia company, Indina, Ethanol from (Tedia company, USA), Hydrochloric acid supplied from (Hopkin and Williams, UK), PEG 4000 supplied from (Sigma Aldrich, USA), HPMC K4M and Carbapol 930 p were purchased from Provizer Pharama,

India), Avicel PH (102) was purchased from (Samra Drug Industry, Iraq). All other chemicals, reagents and solutions used were of analytical grade.

Methods

Determination of Saturated Solubility of Furosemide

The solubility study of furosemide is carried out by adding an excess amount (an amount of active material, more than could be dissolved) which is 10 mg to 20 ml of 0.1 N HCl.

The solutions were stirred in a magnetic stirrer at 37 °C for 24 hrs.

The solutions were then filtered by using Whatman filter paper (0.45) and the absorbance of the prepared dilutions was measured at 274.2 nm using UV - Visible spectrophotometer.[7,8]

The solubility of furosemide was increased by using two methods:

Preparation of Furosemide Solid Dispersion

Preparation of Furosemide Solid Dispersion by Fusion Method

By this method, the polymer (PEG 4000) is heated to a temperature just above its melting point (70 °C) in a water bath; the drug is incorporated in a different drug / polymer ratios as shown in Table 1.

The resultant dissolved drug in the matrix will be obtained to give a homogenized mixture, the melt then solidified (dried in oven at 40 °C, the final solid mass is scratched, pulverized and sieved).[9]

Preparation of Furosemide Complex with ß-Cyclodextrin

Preparation of Furosemide Complex with ß-Cyclodextrin by Kneading Method

This method involve the addition of (50%) aqueous ethanol solution to mixtures of (furosemide: ß-Cyclodextrin) which prepared in different ratios as shown in Table 1, until a creamy homogenous product was obtained, this mixture was transferred to a mortar and kneading for 15 min., then it was dried in an oven under a vacuum at 50 °C until a constant weight was obtained.[8]

Table 1: Formulation Code of Furosemide Solid Dispersions and Complexes

Formulation Code	Method	Furosemide: PEG 4000
FSd1	Solid dispersion (fusion method)	1:1
FSd2		1:3
FSd3		1:5
		Furosemide : ß-Cyclodextrin
FCb1	Complexation (kneading method)	1:1
FCb2		1:3
FCb3		1:5

Evaluation of the Prepared Furosemide Solid Dispersions and Complexes

Determination of Saturated Solubility of Prepared Furosemide Solid Dispersions and Complexes

Similar procedure mentioned previously in saturated solubility of furosemide was used to determine the saturated solubility of furosemide solid dispersions and complexes in 0.1 N HCl and compared to that of pure drug.

Selecting of Best Method and Formulation

The saturated solubility test was used to determine the best method and formulation which would be subjected for further analysis.

Characterization of Best Formula

In-vitro Dissolution Test

A comparison in dissolution profile between pure drug and solubility enhanced best formula (accurately weighted amount (20 mg) of pure drug and an equivalent amount of best formula) was carried out by using USP Dissolution Test Apparatus; Type 2 (paddle type) and 900 ml of 0.1 N HCl was used as dissolution medium for 2 hrs. The temperature of dissolution media was maintained at 37 ± 0.5 °C. The paddle rotation speed was kept at 50 rpm. Aliquots of 5 ml of the sample were withdrawn at every 5, 10, 15, 20, 30, 45, 60, 90, 120 min intervals and the same volume was replaced with pre-warmed fresh dissolution media to maintain sink condition. The samples withdrawn and the absorbance were recorded at 274.2 nm using UV spectrophotometer after filtration through Whatman filter paper.[10]

Characterization by Differential Scanning Calorimetry

Differential Scanning Calorimetry (DSC) is one of the thermal analysis techniques usually used for characterization the thermal behavior of drug substance in pure state and in pharmaceutical mixture. DSC is frequently the pharmaceutical thermal analysis technique of choice because of its ability to provide detailed information about both the physical and energetic properties of substances. The pure drug, polymer and optimized formula were examined by DSC 60 (Shimadzu, Japan) where 5-6 mg samples were placed in aluminum pan at a heating rate of 10 °C/min (in range of 0-250 °C) with purging of dry nitrogen at a constant rate. An empty aluminum pan was used as reference. Indium/Zinc standards were used to calibrate the DSC temperature and enthalpy scale of the instrument. DSC was used to determine thermal behavior including m.p and solid state characterization of furosemide, polymer and best formulation.[11,12]

Characterization by Powder X Ray Diffraction

The extent of crystallinity was determined for pure drug, polymer and solubility optimized best formula using Powder X ray Diffraction (PXRD) system equipped with

Curadiation (λ=1.54060 A°) at a voltage of (40 Kv) and a current of (30 mA).

The instrument was operated in the continuous scan mode and sample were analyzed in the range (5-80°) with a step size of (0.05°) at scanning speed of (5°/min) and (2θ) axis.[13]

Preparation of Stomach Specific Mucoadhesive Tablet

The tablets were prepared by direct compression method, by using two types of polymers (HPMC K4M and Carpabol 930 p) separately as a single polymer and in combination with different ratios as shown in Table 2, the components of each tablet were weight accurately and then passed through 0.36 mm sieve to get uniform particle size, the pure drug/optimized soluble furosemide (solid dispersion) and other ingredients (except lubricant) were mixed in a plastic container for 5 min. Then the lubricant (magnesium stearate) was added and mixed not more than 2 min to coat the particle surface by lubricant evenly, the tablet were compressed by using 8 mm punch and die on single punch tablet machine. The formulated tablets were stored in a tightly closed container until evaluated.[14]

Table 2: Formulations Ingredients of Prepared Mucoadhesive Tablets of Furosemide

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Furosemide	20	-----	-----	------	------	-----
Solid dispersion	-----	80	80	80	80	80
HPMC K4M	24	24	-----	16	12	8
Carpabol 930 P	------	------	24	8	12	16
Avecil PH 102	52	52	52	52	52	52
Mg stearate	4	4	4	4	4	4
Total weight	160	160	160	160	160	160

Evaluation of Prepared Stomach Specific Mucoadhesive Tablet

Determination of Various Physicochemical Parameters for Prepared Mucoadhesive Tablets

The thickness of tablets prepared was calculated using Vernier caliper.[15] The hardness of the tablets was determined using electrical hardness tester. It is expressed in Kg/cm^2. The hardness test was performed in which five tablets from each formula were tested randomly and the average reading ± SD was recorded.[16] The friability test was done by placing 20 pre-weighed tablets in the friabilator which was then operated for 25 rpm for 4 minutes; the tablets were then dusted and reweighed. Tablets that lose a maximum of not more than 1% of their weight are generally considered acceptable.[17] Furthermore, the weight variation can be tested by taking twenty tablets were weighed individually and the average weight was determined. The percentage deviation was calculated and checked for weight variation.[18]

Determination of Percent Drug Content (Content Uniformity)

The content uniformity was done by weighing and powdering twenty tablets. Weigh accurately an equivalent to 20 mg of pure drug and an equivalent to solubility enhanced best formula and placed in 100 ml volumetric flask then diluted with 0.1N HCl. Filtered the solution with Whatman filter 0.45, an ultraviolet UV - Spectrophotometric method based on the measurement of absorbance at 274.2 nm was used for the estimation of furosemide content.[19]

Determination of Swelling Index (Percentage of Hydration)

The swelling behavior of the prepared tablets was studied by measuring the weight gain, each tablet was placed on a microscope slide in a petridish containing 0.1N HCl at 37 °C ± 0.5, after each time interval, the tablet was removed from the petridish and weigh again after it was blotted with tissue paper to remove excess of water, the experiment was performed in triplicate at each time point for total duration of 6 hrs, the following formula was used to measure the swelling index of prepared tablets:[20]

Swelling Index of the Tablet (%) = ($W_t - W_0 / W_t$) x 100

Where, W_0 =Initial weight of the tablet, W_t = weight gain by the swollen tablet

Measurement of *EX-Vivo* Mucoadhesive Strength

A modified physical balance was used for determining *EX-Vivo* mucoadhesive strength. Sheep stomach mucosa was obtained from slaughter house and used as a model mucosal membrane, the stomach mucosa membrane was excited and washed (equilibrated at 37 ± 1 °C for 30 min in 0.1N HCl medium before mucoadhesion evaluation study started. The mucosa was stuck on the bottom of the petridish by cyanoacrylate glue such that the mucosal surface faced upward and the 0.1 N HCl is added till it reached the surface of mucosal membrane and kept it moist. The stomach specific mucoadhesive tablet was stuck to the lower side of a glass stopper with cyanoacrylate adhesive. The two sides of the balance were made equal before the study, by keeping a 10 g weight on the right-hand pan. A weight of 10 g was removed from the right-hand pan, which lowered the pan along with the tablet over the mucosa. The balance was kept in this position for 5 minutes contact time; a force was applied to the left pan of balance by pouring water drop wise to the beaker till complete detachment of tablet achieved. The mucoadhesive strength represents the amount of water added minus the weight of the preload.[21,22]

***In-vitro* Drug Release Test**

Similar procedure and conditions mentioned for studying the *in-vitro* release of furosemide solubility optimized

formula were used, the duration of study 5 hrs, where aliquots of 5 ml of the sample were withdrawn at 0.25, 0.5, 1, 2, 3, 4 and 5 hrs intervals for each formulation and the same volume was replaced with pre-warmed fresh dissolution media to maintain sink condition. The samples withdrawn and the absorbance were recorded at 274.2 nm using UV - spectrophotometer after filtration through Whatman filter paper.[23]

Measurement of *EX- Vivo* Gastric Retention Time of Selected Mucoadhesive Tablet

The stomach mucosal tissues of the sheep were fixed on internal side of beaker with cyanoacrylate glue. Each tablet of selected formula that previously wetted with 0.1 N HCl was attached to the stomach mucosa by applying a light force with fingertip for 20 seconds. The beaker was filled with 900 ml of 0.1 N HCl and placed on magnetic stirrer and kept at 37 °C after 2 min. a stirring rate of 50 rpm was applied until erosion or complete detachment of tablet occurred.[24]

Statistical Analysis

The results of the experiments are given as a mean values ± standard deviation (SD) and were analyzed according to one-way analysis of variance (ANOVA) at which significant results ($p<0.05$) and non-significant ($p>0.05$).

RESULTS AND DISCUSSION

Solubility of Furosemide

The saturated solubility results of pure powder in addition to (solid dispersion and complexes) of furosemide were shown in Table 3, the measured solubility of furosemide powder in 0.1 N HCl (pH=1.2) is 1 mg /100 ml (0.01 mg/ml) indicating that the drug is poorly soluble compound in this buffer, this is due to acidic nature of the drug since furosemide is a weak acid drug which in acidic medium tend to be in the unionized form (lipophilic nature). The solubility studies revealed that there is a significant increase ($p<0.05$) in drug solubility by using two solubility methods mentioned earlier in comparison to pure powder, it was found that the solid dispersion method (furosemide/PEG 4000 in different ratios 1:1 and 1:3) enhancing the furosemide solubility significantly ($p<0.05$) as the ratio of PEG 4000 increased, this is because hydrophilic carriers are known to interact with drug molecules, mainly by electrostatic forces and occasionally by other types of forces like intermolecular hydrogen bonds.[25,26]

While the addition of PEG 4000 in higher ratio (1:5) did not show additional improvement in solubility in comparison to other lower ratios (1:1 and 1:3), this may be attributed to the viscous layer formed around the solid particles due to increase PEG 4000 concentrations as a consequences result reduction in diffusion coefficient and dissolution of drug.[27]

In complexation method the results showed that the solubility of the drug was found to be increased considerably by complexation of furosemide with ß-cyclodextrine in different ratios (1:1,1:3 and 1:5), as the ratio of ß-cyclodextrine increased the solubility was increased, the increase in solubility may be due to Cyclodextrin unique feature with lipophilic inner cavity and hydrophilic outer surface that resembles a molecular container which holds non polar, non-ionic guest molecules in its inner cavity. This results the formation of inclusion complex that confers exclusive property (enhanced solubilization capacity) on guest molecules due to hydrophilic outer surface of molecular container.[28]

Table 3: Saturated Solubility of Pure Powder, Solid Dispersions and Complexes of Furosemide in 0.1N HCl (pH 1.2).

	Concentration (mg/ml)
Furosemide Pure Powder	0.01
FSd1	1.44
FSd2	2.91
FSd3	2
FCb1	1.022
FCb2	1.62
FCb3	1.89

Selecting Best Method and Best Formula

Solid dispersion with ratio 1:3 formula (FSd2) was chosen as the best method and formula since it showed higher drug solubility than complexation method and other prepared ratios therefore, further characterization of this formula was done.

Characterization of the Best Formula

In-vitro Dissolution Test

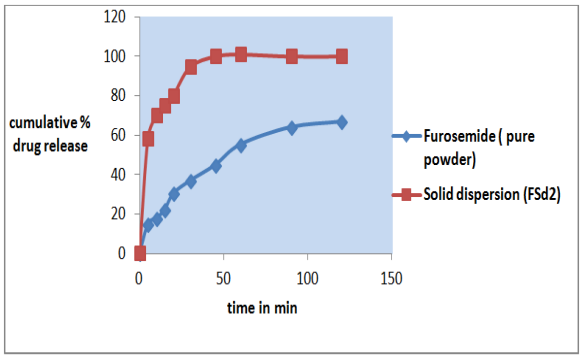

Figure 1: Comparison in Drug Release Profile between Pure Drug and Solid Dispersion in 0.1 N HCl at 37°C.

It is evident that from the Figure 1 furosemide solid dispersion showed significantly higher dissolution rate ($p<0.05$) in comparison to furosemide as pure drug, this is may be due to several factors such as particle size reduction of the drug, formation of higher energy metastable state with higher degree of amorphization of the drug, improved drug's wetting properties, local solubilization of the carrier at the diffusion layer,

increased porosity, and the formation of intermolecular hydrogen bonding between the drug and the carrier.[29-31]

Differential Scanning Calorimetry (DSC)

The thermograms of furosemide and PEG4000 that shown in Figure 2 indicate their crystalline nature by exhibiting one endothermic peak corresponding to the melting point of the drug and the carrier respectively.

The presence of single endothermic peak in the thermogram of solid dispersion at 49.47 °C around the polymer m.p, and the absence of m.p of drug in solid dispersion thermogram could be attributed to the possible dissolution of the drug in the molten carrier during heating cycle in DSC analysis or might also due to the fact that drug undergo transformation from its crystalline form to amorphous form in the solid dispersion formulation which can be further supported by PXRD results.[32,33]

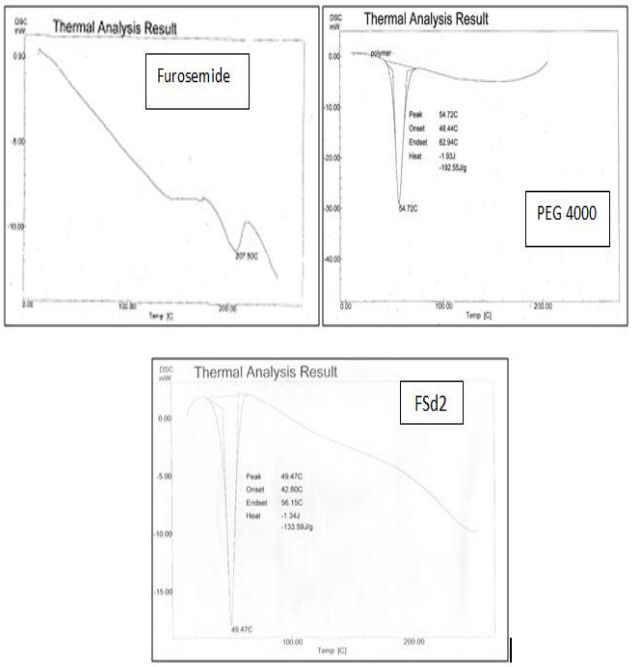

Figure 2: DSC Thermograms of Pure Furosemide and PEG 4000 and FSd2

Powder X-Ray Diffraction (PXRD)

The solid state characterization of drug, PEG 4000 and solid dispersion were investigated using XRD to find out crystalline nature of furosemide and FSd2 (1:3 PEG4000).

The diffraction spectrum of pure furosemide showed that the drug was crystalline in nature as it was demonstrated by numerous peaks.

As shown in Figure 3 some changes in the peak positions of furosemide were observed in solid dispersion. Peak intensity was also decreased in solid dispersion.

Highest peak intensity in case of pure furosemide was 1475 counts; on the other hand it was only 76 in case of solid dispersion.

The relative reduction of diffraction intensity of furosemide in solid dispersion at these angles suggests that the size of the crystals was reduced.

The results of this study imply that furosemide is present in partially amorphous or microcrystalline form in the solid dispersion.

Also there is no appearance of new diffraction peaks which rules out any chemical interaction between the components or the existence of any other type of crystals.[34]

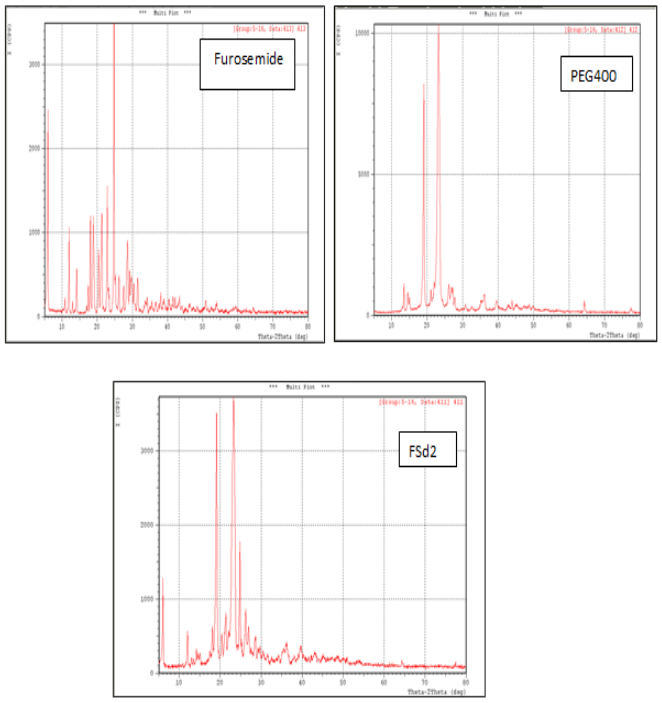

Figure 3: X-ray Diffraction Patterns of Pure Furosemide, PEG 4000 and FSd2

Evaluation of Prepared Stomach Specific Mucoadhesive Tablets

Physicochemical Properties and Percent Drug Content of Prepared Furosemide Mucoadhesive Tablets

All formulations of tablets (F1-F6) were evaluated for the physical properties, the thickness was in the range of (3.46-3.58) mm, the hardness were in the range of (5.1-8)kg/cm^2 indicating that the tablets were of adequate strength property to resist handling and mechanical stress.

Friability test shows that the weight loss resulted was lower than 1% (for all tablets indicating good compactness and mechanical resistance), weight variation evaluation showed that all the prepared tablets met the USP requirements.

Drug content was in the range (90.1-99.8) % indicating that furosemide was uniformly distributed in all prepared formulas as shown in the Table 4.

Table 4: Physicochemical Parameters and Content Uniformity of Prepared Furosemide Mucoadhesive Tablets

FormulaC ode	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight Variation	Drug Content (%)
F1	3.52 ± 0.014	5.1	0.25 ± 0.13	Passed	99.8
F2	3.5 ± 0.023	5.2	0.28 ± 0.23	Passed	92.7
F3	3.58 ± 0.027	7.2	0.31 ± 0.12	passed	90.1
F4	3.5 ± 0.003	6.1	0.21 ± 0.29	Passed	98.5
F5	3.48 ± 0.076	7	0.30 ± 0.15	Passed	90.5
F6	3.46 ± 0.021	8	0.36 ± 0.28	passed	95.3

Swelling Index (Percentage of Hydration)

Adequate swelling is a crucial attribute for consistent, extended drug release and effective mucoadhesion characteristics; all the tablet matrices were stable throughout the period of swelling, without any disintegration being observed. The percentage of hydration of the prepared formulations ranged from 30 % to 50 % at the end of 6 hrs. The swelling index of prepared formulations is shown in figure 4, formula F3 which contained carpabol 930 p as a single polymer showed maximum swelling index. Furthermore, incorporation and increasing the amount of carpabol 930 p in formulas F4, F5 and F6 the swelling index increased significantly (P<0.05) this is attributed to the -COOH group of carpabol which become hydrated forming hydrogen bonds with the imbibing of water quickly and therefore, extending the polymer chain.[35] Formula F1 showed significantly (P<0.05) the lowest swelling index among other formulas this is related to poor aqueous solubility of pure Furosemide powder and hence less water uptake.

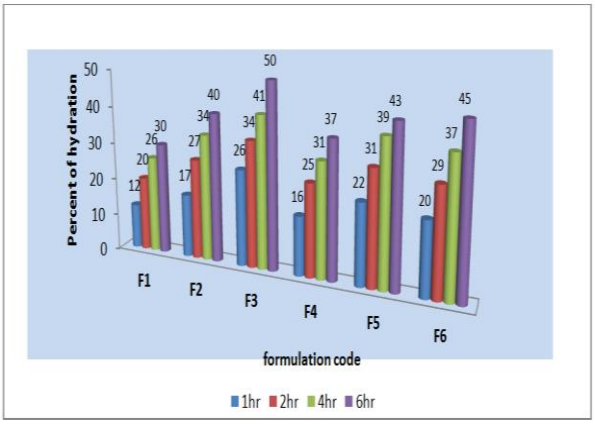

Figure 4: Swelling Index Profile of Prepared Mucoadhesive Tablets (F1-F6)

***Ex-Vivo* Mucoadhesive Strength**

Figure 5 shows the mucoadhesive strength of prepared formulas (F1-F6), formula F3 containing carpabol 930 p as a single polymer showed significantly higher (p<0.05) mucoadhesive strength than F2 which contains HPMC K4M, this is attributed to that hydrogels are known to swell readily when come in contact with hydrated mucous membrane. The water sorption reduces the glass transition temperature below the ambient conditions and hydrogels become progressively rubbery due to uncoiling of polymer chains and subsequent increased mobility of the polymer chains. This glass-rubbery transition provides hydrogel plasticization resulting in large adhesive surface for maximum contact with mucin and flexibility to the polymer chains for interpenetration with mucin. Furthermore, Increasing the amount of carpabol 930 p as in F4, F5 and F6 showed significant (p<0.05) increase in mucoadhesion strength this is related to increasing the polymer amount may provide more adhesive sites and polymer chains for interpenetration with mucin, resulting consequently in the augmentation of bioadhesive strength.[36,37] This statement was supported by the results of the swelling index. Both swelling index and bioadhesion were found to be directly proportional. While formula F1 that contained pure furosemide it showed significantly (p< 0.05) lower mucoadhesive strength than F2 that contained solid dispersion may be due to reduced hydration property and hence the swelling index related to poor solubility of the drug.

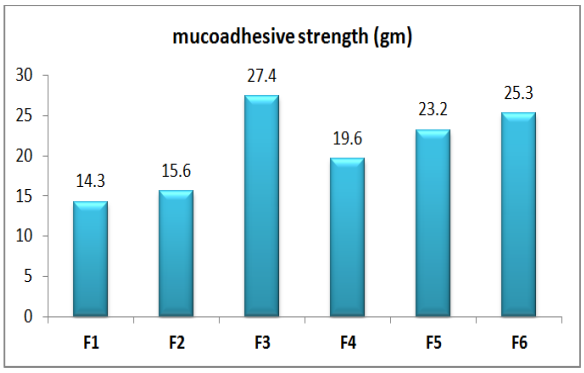

Figure 5: Mucoadhesive Strength of Prepared Mucoadhesive Tablets (F1-F6)

***In-vitro* Drug Release**

Figure 6 illustrates the in-vitro drug release of prepared furosemide mucoadhesive tablets formulas (F1-F6), Formula F3 showed significantly (p<0.05) lower drug release (32%) after 5 hrs in comparison to F2, the drug release after 5 hrs was found (96%), incorporation and increasing the amount of carpabol 930 p in formulas F4 and F6 lead to significant (p<0.05) decrease in drug release (79.9%) and (60.6%) respectively. This is attributed to the high swelling index upon hydrated with

water which leads to increase diffusion path length and retard drug release.[38] While formula F5 that contained equal amounts of both polymers (1:1) the release showed retardation more than F6 (44.3%) this is maybe due to synergistic increase in the viscosity as a result of competent water uptake of HPMC K4M and carbopol 930 P resulting in the formation of strong gel layer and consequently slower diffusion and erosion rate.[39]

Formula F2 showed higher in-vitro drug release than F1 which indicated that the enhancement in the dissolution of drug from solid dispersion samples is maintained after manufacturing the solid dispersion into tablets.

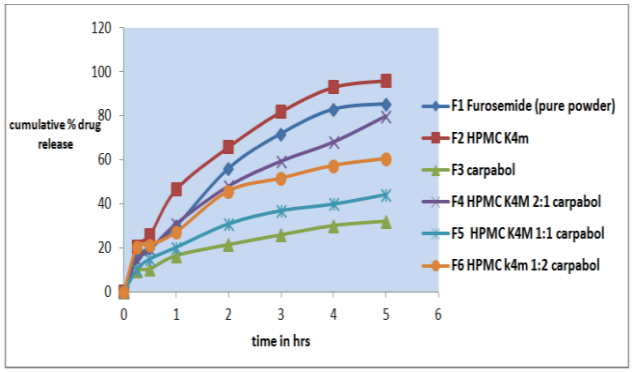

Figure 6: *In-vitro* Drug Release of Prepared Mucoadhesive Formulas (F1-F6)

EX–vivo Gastric Retention Time for Selected Tablet

The selected Formula F2 was subjected to *EX-Vivo* gastric retention time as this formula showed promising results in accordance to *in-vitro* drug release in addition good swelling index and mucoadhesion strength, it was found that the formula F2 resided for 7.10 hr on sheep gastric mucosa witch is satisfactory for *in-vitro* drug release for 5 hrs, thus maintaining gastric retention and achieving the aim of the study by mucoadhesion character.

CONCLUSION

The overall study revealed that solid dispersions and complexes of furosemide were successfully prepared by kneading and fusion methods respectively. The solid dispersion has more pronounced effect on solubility than complexation. Therefore; it was selected as best method for enhancing the solubility of furosemide. The presence of amorphous form in solid dispersion was confirmed by DSC, PXRD, and was reflected in the significant improvement in rate as well as the extent of *in-vitro* drug dissolution. Gastro retentive mucoadhesive tablet can be prepared successfully by direct compression method using two polymers alone and in combinations with different ratios (HPMC K4M and carpabol 930 p), formula F2 which contained HPMC K4M as a single polymer chosen as the selective mucoadhesive tablet, since it showed a high *in-vitro* drug release at the end of 5 hrs, good swelling index, suitable mucoadhesive strength that give convenient EX-Vivo gastric retention time and thus will increase the gastric transit time, this lead to improvement in absorption and as a consequences the bioavailability of drug.

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