# Site Specific Oral Modified Release System of Furosamide Solid Dispersion with microenvironment pH modulation

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**Abstract**

Furosemide is loop diuretics belonging to BCS class IV category, which is comparatively more difficult to formulate as effective oral drug delivery system owing to its restrictive solubility and permeability characteristics. In present work, solubility enhancement and improvement in permeability of furosemide was done by solid dispersion technique. Moreover, an attempt to overcome limited permeability issue was made by a logical technique of keeping the dosage form in the proximity of absorbing surface of GI tract in order to enhance its probability of being absorbed. Final modified release delivery system was in the form of capsule filled with 4 mucoadhesive minitabs having around 4 mm diameter and <3mm thickness. Solid dispersions was prepared using two different carriers - PVP K 30 and PEG 6000 at different drug:carrier ratios. Best solid dispersion was further utilized for preparing mucoadhesive minitabs. Moreover, considering pH dependent solubility of Furosamide, a basic pH microenvironment was created inside tablet matrix to further felicitate drug solubility and release during initial few hours. Optimization of the formulation was done by using Central Composite Design with independent variables -PEO WSR 303 and HPMC K100 M; and dependent variables - % drug released at four different time points up to 24 h. The release profile as a response was carried out for 24 hrs at different time. Overlay spectra was plotted and in design space the value of %PE was found to be less than 5% revealed the best fit model. Further more solid dispersion of PVP K 30, PEG 6000 were prepared and checked for solubility enhancement and finally, the developed solid dispersion incorporated in to mucoadhesive tablet. The outcome of experimental design

revealed that both the formulation variables PEO 303 and HPMC K100 M have significant impact on the dependent response like dissolution at 2 hrs, 6 hrs, 12 hrs, 18 hrs, and 24 hrs. ANOVA revealed that the derived models were significant at each response of dissolution. Solid dispersion prepared by Drug: PVP K-30 ratio of 1:5 showed increment in the solubility of Furosemide. Optimization formulation derived from the experimental design showed an extended release profile up to 24 hrs with sufficient adhesive strength to retain the dosage form in stomach as compared to the plain drug. However, the logic applied for keeping a dosage form in the proximity of GI tract surface can only be proved by *in vivo* studies. Further pharmacokinetic studies on such formulations are required in to support *in vitro* findings. Moreover, *in vivo* studies in the presence of permeation enhancer need to be conducted to overcome the low permeability issue of such drugs.

**Key words:** Furosemide, Mucoadhesive Minitab, solid dispersion, pH modulator, and BCS Class IV

## 1. Introduction

BCS class IV drugs are well known to the pharma industry for its low bioavailability concern. There is need to improve the solubility& permeability of BCS class IV drug to enhance its bioavailability[1]. The drugs of BCS Class IV category have major concern of high first pass metabolism with faster rate elimination e.g. Furosemide. 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[2]. One of the major causes of low oral bioavailability of furosemide is solubility. 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.

Formulations developed for mucoadhesive drug delivery should be small and flexible enough to be acceptable for patients and should not cause irritation. Other desired characteristics of a mucoadhesive dosage form include high drug loading capacity, controlled drug release (preferably unidirectional release), good mucoadhesive properties, smooth surface, tastelessness, and convenient application. The uptake of drugs is often limited by the short contact time between the formulation and the absorption membrane and by a fast washout. Mucoadhesive drug delivery systems interact with the mucus layer covering the mucosal epithelial surface, and mucin molecules using mucoadhesive polymers, however, the residence time of the dosage form on the mucosa can be significantly increased[4]. The pH of the medium and pKa of the drug may affect the release profile. Weakly acidic drugs like Furosemide with pH-dependent solubility can experience problem on release from controlled release dosage forms. Penetration of fluid with changes in pH may cause conversion of more ionizable drug to a less soluble form and therefore diffusion of the drug from the matrix. Because of which, formulation of such drugs for oral administration can be expected to result

in particularly variable release rates with changes in pH of the surrounding fluids[5]. The objective of transmucosal formulation designs for weakly acidic drug is enhancing the bioavailability and reduces variability. A polymer, PolyOX WSR 303 has been reported to produce pH independent release of a weakly acidic drug[6], Furosemide from a hydrophilic HPMC-based mucoadhesive tablet where PolyOX WSR 303 has altered the pH.

The development of sustain release dosage form can achieve the aim of releasing the drug slowly for a long period but this is not sufficient to get sustained therapeutic effect. They may be cleared from the site of absorption before emptying the drug content. Instead, the mucoadhesive dosage form will serve both the purposes of sustain release and presence of dosage form at the site of absorption[7]. In this regard, our review is high lighting few aspects of mucoadhesive drug delivery systems.

Moreover, to facilitate quick absorption of dissolved molecules, the dosage form needs to be in close proximity of the absorbing surface of GI tract[8]. So, in present study, mucoadhesive formulation of furosemide has been designed to improve the solubility & permeability. Based on solubility data of furosemide solid dispersion technique was adopted by taking different concentration of PVP K-30 and PEG -6000 along with pH modular using hot melt method[9]. This developed solid dispersion further formulated in mucoadhesive disc by compression with higher contact surface. Finally modified release dosage form was in the form of capsules filled with mucoadhesive mini-tablet having around 4 mm diameter and <3 mm thickness. In this work, a molecular dispersion of drug in a polymer matrix was formulated, and then compressed as mucoadhesive mini-tab which was filled in a suitable capsule shell. The formulations were characterized and optimized. The optimized formulation was also evaluated for *in-vitro* release studies.

The aim of the study was to enhance the solubility of furosemide by making its solid dispersion, using hot melt method and then incorporates it into stomach specific mucoadhesive mini tablet dosage form, by adopting central composite design for optimization and developed formulation having pH modulators which was evaluated for controlled release of the drug for 24 hours. Thus, it may be improving furosemide absorption and bioavailability.

## 2. Material and Methods

The following pharmaceutical materials were used as received for this study, without further processing or purification. Furosemide was obtained as a gift sample from Rivera Pharma , Surat, Gujarat-India , PVP K-30 was obtained from Chemdyes Corporation, Rajkot, Gujarat-India and Microcrystalline cellulose (Avicel PH 200), Polyethylene oxide WSR 303, PEG -6000, HPMC K100M, Sodium bicarbonate were purchased from Yarrow Chem Pvt. Ltd, Mumbai, India. Piperin purchased from Greenwell Overseas, Ahmedabad, India.

### Quantification of Furosemide [10]

A double beam UV spectrophotometer (UV-1800, Shimadzu, Japan) was used to measure Furosamide in bulk samples and all *in vitro* studies. A known amount of Furosamide (100 µg/mL) was dissolved in suitable solvents, followed by filtration and kept in quarts cell for

analysis against solvents as blank reading. Suitable dilutions were prepared (2-12 µg/ml) and linearity was observed. Samples were prepared and checked for 3 days for inter and intraday variability.

**Optimization of mucoadhesive tablets using Central composite design**

A central composite design was used to systematically study the influence of the individual and combined effect of independent variables i.e. numeric factors which can control by us in formulation[11]. They are X1 and X2. From these independent variables affecting on dependent variables i.e. PEO 303 (mg) and HPMC K-100M(mg). In present study, two independent factors were evaluated, and experimental trials were conducted at all $16^{th}$ possible combinations and recorded their dependent variables. Statistical model central composite design was selected as two independent variables to study in development of this dosage form in order to find their individual and combined effects on the dependent variables. Response surface and contour plots shows the interaction between different variables. A statistical model, which consists of interactive and polynomial terms, was utilized to evaluate the responses. The responses were analyzed using analysis of variance (ANOVA) and the individual response parameters were evaluated using F test and polynomial equation was generated for each response using multiple linear regression analysis. Response surface methodology (RSM) is characteristically employed to relate a response variable to the levels of the input[12].

**Table 1. Batch code variable levels in coded form actual quantity of polymer**

| Code | Polymer | -1 | 0 | +1 |
|---|---|---|---|---|
| X1 | PEO 303 | 5.00 | 7.50 | 10.00 |
| X2 | HPMC K-100M | 6.00 | 9.00 | 12.00 |

Considering PEO WSR 303 polymer level 7.50 mg and HPMC K-100M 9.00 mg at middle step at position "0". A full factorial design (central composite design) was employed to study the effect of independent variables, i.e., PEO 303(X1) and HPMC K100M (X2) on dependent variables drug released 2 hr,6 hr,12 hr,18 hr. and 24 hr. Contour or RSM plots for each response were generated using the DESIGN EXPERT (STAT-EASE) demo version software.

**Table 2. Formulation composition of Central composite design batches**

| Sr. No. | Ingredients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 | F13 | F14 | F15 | F16 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Furosemide Sodium | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 |
| 2 | Polyox WSR 303 | 7.50 | 3.96 | 10.00 | 7.50 | 7.50 | 7.50 | 7.50 | 5.00 | 7.50 | 7.50 | 7.50 | 7.50 | 11.04 | 5.00 | 10.00 | 7.50 |
| 3 | HPMC K100M | 9.00 | 9.00 | 6.00 | 13.24 | 9.00 | 9.00 | 4.76 | 12.00 | 9.00 | 9.00 | 9.00 | 9.00 | 9.00 | 6.00 | 12.00 | 9.00 |
| 4 | Microcrystalline Cellulose (Avicel PH 200) (q.s.) | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 |
| 5 | Magnesium stearate | 0.60 | 0.60 | 0.60 | 0.60 | 0.60 | 0.60 | 0.60 | 0.60 | 0.60 | 0.60 | 0.60 | 0.60 | 0.60 | 0.60 | 0.60 | 0.60 |
| Total weight of tablet | | 40.0 | 40.0 | 40.0 | 40.0 | 40.0 | 40.0 | 40.0 | 40.0 | 40.0 | 40.0 | 40.0 | 40.0 | 40.0 | 40.0 | 40.0 | 40.0 |

Sifted materials Furosemide, Microcrystalline Cellulose (Avicel PH 200), Polyethylene oxide WSR 303, HPMC K100M were added into the suitable capacity of octagonal blender & mixed for 20 minutes at 20 RPM to get the homogeneous mixture. To this pre-sifted magnesium stearate was added and mixed for 10 min to lubricate the blend. Lubricated blend was subjected to compression. Compression done using Cadmach 12 station single rotary compression machine with B tooling 4 mm round shaped flat faced biconvex punches plain on both side. Prepared Mucoadhesive tablets were evaluated for weight and content uniformity, hardness, thickness, friability and disintegration characteristics as per pharmacopoeial specifications. Produced Mucoadhesive tablets were filled into the hard gelatin capsule shell (HGCS). Each HGCS of size 4 was filled with four Muco-adhesive tablets. In addition to the above properties prepared tablets, formulations were also evaluated for Average weight, thickness, hardness and *in vitro* release, bio-adhesion.

**Preparation of Solid dispersion of Furosamide with different polymeric carriers**

The Solid dispersion technology is commonly used method for enhancement of solubility with various preparation methods, parameters and polymers. According to literature Furosemide is reported to be an “almost insoluble drug in water,” with a “natural” solubility round 18 µg/ml at 30°C at pH 7.0[13]. In hot melt method, the carriers such as PVP-K-30/PEG 6000 were selected based on the preliminary solubility study. The shifted drug to polymer ratio (weight basis) was kept 1:0.1, 1:0.5 and 1:1.Drug and polymer carrier mixture were mixed with ethanol (85%v/v) to obtain slurry and were kneaded thoroughly for 60 minutes in glass mortor. The paste formed was dried under vacuum (Conaform Vaccume dryer, Patterson Industries, Canada.) for 24 hrs. The solid dispersions obtained from this method were tacky enough. The resulting powder was passed through sieve #60.

*Comparative solubility study of drug and solid dispersion*

Solubility of Furosamide and its solid dispersions in water was measured according to the method reported by Higuchi and Connors[14]. Furosamide and its solid dispersions were separately transferred to screw-capped vials containing 10 ml distilled water. The contents were stirred on an electromagnetic stirrer (Remi, India) at 37 °C for 72 h and 300 rpm. After reaching equilibrium, samples were filtered through a 0.22-µm membrane filter, suitably diluted with distilled water (if required), and analyzed for drug solubility profiles.

**Incorporation of solid dispersion in mucoadhesive tablet[15]**

Solubility behavior is one of the most challenging aspects for drug commercialization or one of the main reasons for a drug that does not reach to its full potential. So here, the developed solid dispersion of furosemide was replaced with furosemide API in mucoadhesive tablet, which was previously optimized by central composite design. Prepared batches SD1 to SD 12 (Table 3) were further evaluated for hardness, weight variation, thickness and *in vitro* release studies. Moreover, sodium bicarbonate was also incorporated in this tablet formulation to maintain the basic microenvironment to assist further drug dissolution and release from the matrix core. Produced Mucoadhesive tablets were filled into the hard gelatin capsule shell (HGCS). Each HGCS of size 4 was filled with four mucoadhesive tablets.

**Table 3. Composition of mucoadhesive minitablets containing solid dispersion and pH modulator**

| Sr. No | Ingredients | SD1 | SD2 | SD3 | SD4 | SD5 | SD6 | SD7 | SD8 | SD9 | SD10 | SD11 | SD12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1.** | Furosamide (in the form of solid dispersion prepared with carrier PVP K-30 or PEG 6000 as mentioned below) | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 |
| **2.** | PVP K-30 | 0.50 | 2.50 | 5.00 | - | - | - | 0.50 | 2.50 | 5.00 | - | - | - |
| **3.** | PEG-6000 | - | - | - | 0.50 | 2.50 | 5.00 | - | - | - | 0.50 | 2.50 | 5.00 |
| **4.** | PolyOX WSR 303 | 7.50 | 7.50 | 7.50 | 7.50 | 7.50 | 7.50 | 7.50 | 7.50 | 7.50 | 7.50 | 7.50 | 7.50 |
| **5.** | Sodium biCarbonate | - | - | - | - | - | - | 10 | 10 | 10 | 10 | 10 | 10 |
| **6.** | HPMC K100M | 12.0 | 12.0 | 12.0 | 12.0 | 12.0 | 12.0 | 12.0 | 12.0 | 12.0 | 12.0 | 12.0 | 12.0 |
| **7.** | Microcrystalline Cellulose (Avicel PH 200) (q.s.) | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 |
| **8.** | Magnesium stearate | 0.60 | 0.60 | 0.60 | 0.60 | 0.60 | 0.60 | 0.60 | 0.60 | 0.60 | 0.60 | 0.60 | 0.60 |
| Total weight of tablet (mg) | | 60.0 | 60.0 | 60.0 | 60.0 | 60.0 | 60.0 | 60.0 | 60.0 | 60.0 | 60.0 | 60.0 | 60.0 |

## 3. Result and discussion

Under the UV spectrophotometric studies, it was found that the $\lambda_{max}$ for furosemide was observed at 276 nm as shown in figure 1. and drug content in bulk and *in vitro* studies was analyzed at this wavelength. A standard curve was prepared, and linearity function was applied having regression equation Y = 0.0979X + 0.0232. The limit of detection (LOD) and The limit of quantification (LOQ) were estimated.

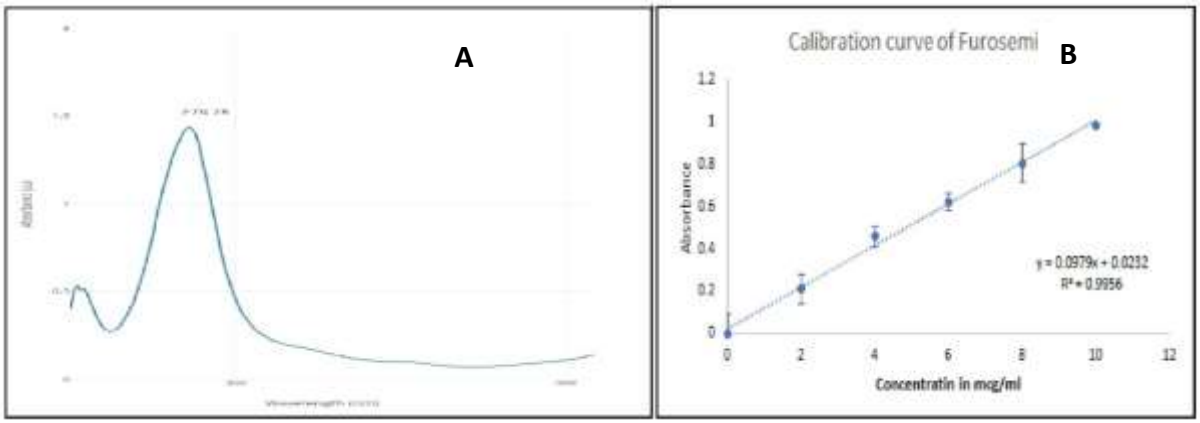



**Figure 1. A. UV visible spectra B. Calibration curve of Furosemide**

### Optimization of Mucoadhesive tablet using Central composite design

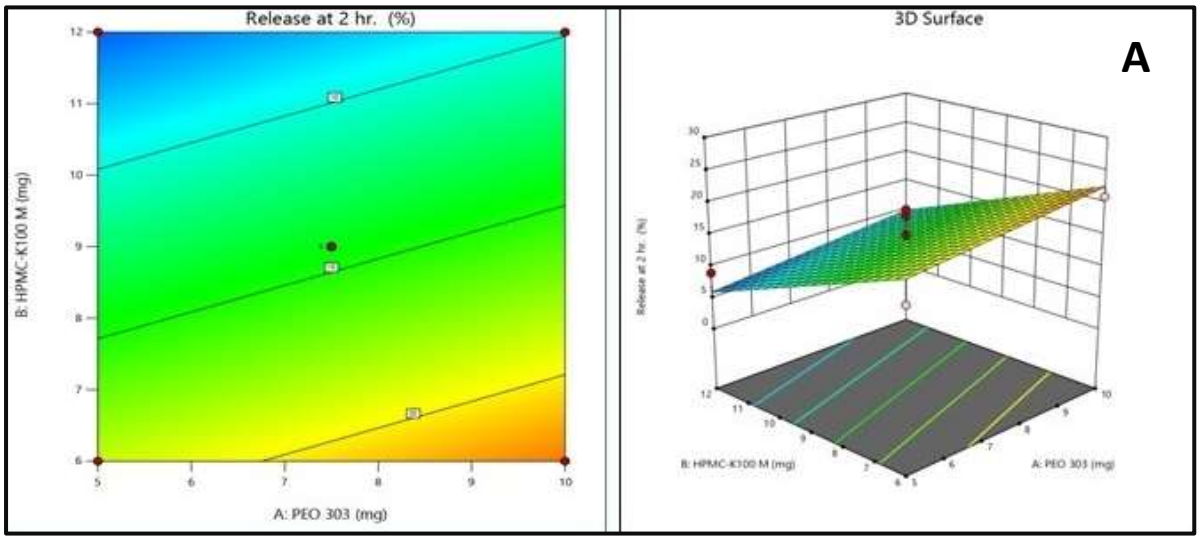
All 16 runs were tried with different ratio of PEO 303 (mg) and HPMC K-100M(mg) and evaluated for its responses and the results of drug release studies at 2 hrs, 6 hrs, 12 hrs, 18 hrs and at 24 hrs as shown in following table.

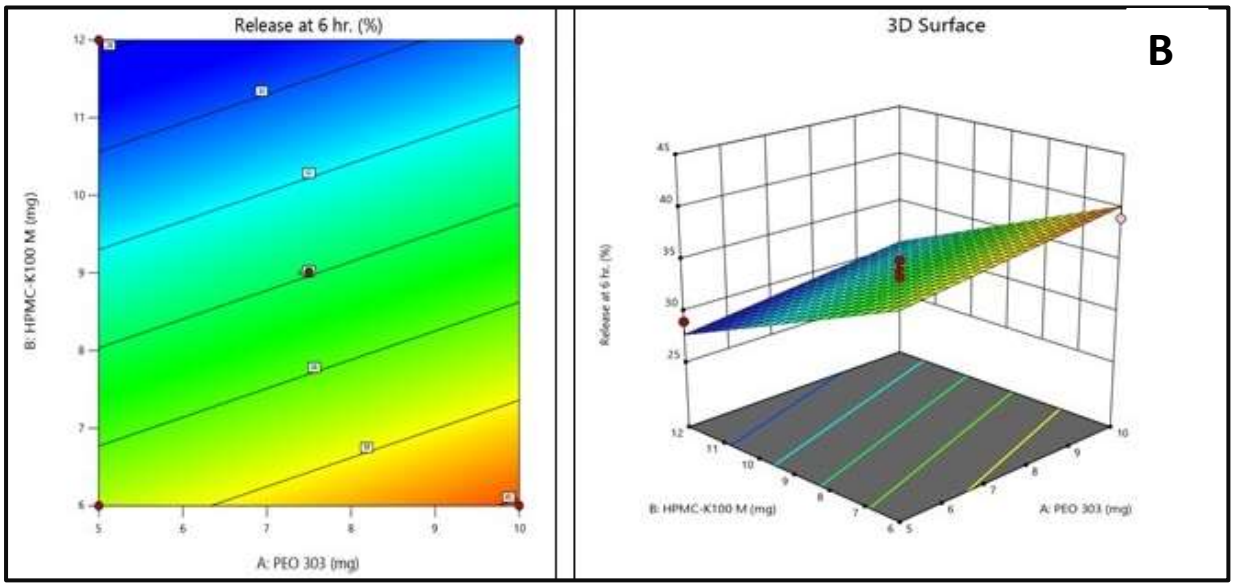
**Table 4 Proposed Runs of Central composite design and its Responses**

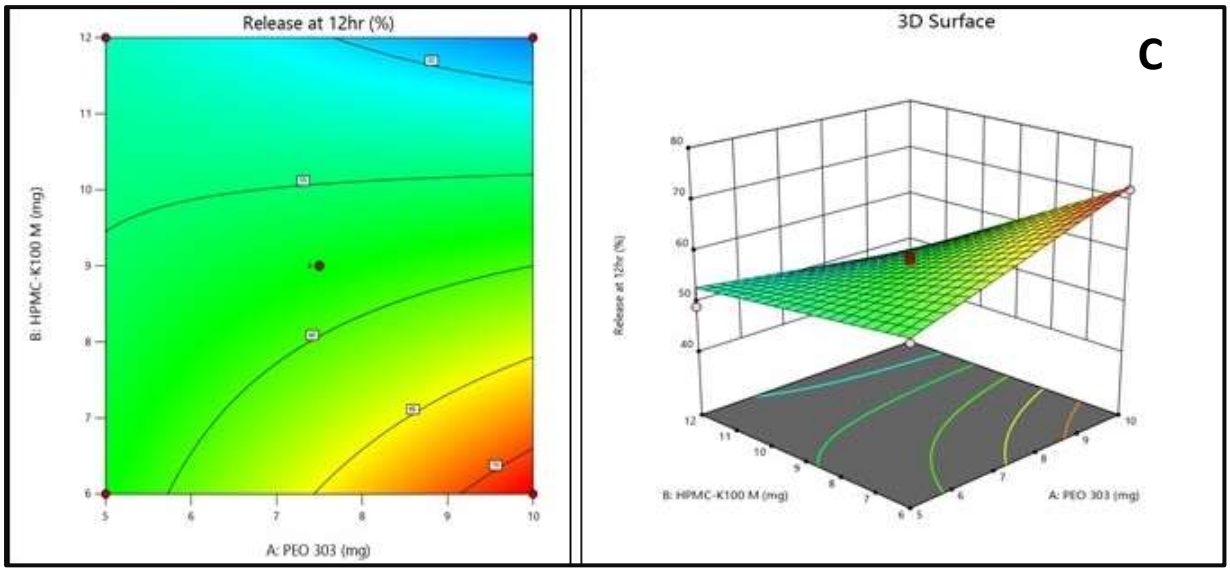
| Run | Trial No. | Space Type | Factor 1 | Factor 2 | Response 1 | Response 2 | Response 3 | Response 4 | Response 5 |
|---|---|---|---|---|---|---|---|---|---|
| | | | A:PEO 303 | B:HPMC-K100 M | Release at 2 hr. | Release at 6 hr. | Release at 12hr | Release at 18 hr | Release at 24 hr |
| | | | mg | mg | % | % | % | % | % |
| 1 | T1 | Center | 7.5 | 9 | 14 | 32 | 59 | 90 | 103 |
| 2 | T2 | Axial | 3.96447 | 9 | 10 | 31 | 60 | 97 | 99 |
| 3 | T3 | Factorial | 10 | 6 | 21 | 39 | 72 | 99 | 102 |
| 4 | T4 | Axial | 7.5 | 13.2426 | 4 | 29 | 51 | 80 | 93 |
| 5 | T5 | Center | 7.5 | 9 | 19 | 31 | 55 | 90 | 99 |
| 6 | T6 | Center | 7.5 | 9 | 15 | 32 | 57 | 93 | 101 |
| 7 | T7 | Axial | 7.5 | 4.75736 | 25 | 41 | 68 | 99 | 101 |
| 8 | T8 | Factorial | 5 | 12 | 9 | 29 | 49 | 94 | 99 |
| 9 | T9 | Center | 7.5 | 9 | 18 | 34 | 59 | 91 | 100 |
| 10 | T10 | Center | 7.5 | 9 | 13 | 35 | 58 | 96 | 99 |
| 11 | T11 | Center | 7.5 | 9 | 14 | 33 | 57 | 97 | 101 |
| 12 | T12 | Center | 7.5 | 9 | 13 | 35 | 52 | 99 | 103 |
| 13 | T13 | Axial | 11.0355 | 9 | 19 | 40 | 66 | 84 | 102 |
| 14 | T14 | Factorial | 5 | 6 | 15 | 40 | 57 | 88 | 98 |

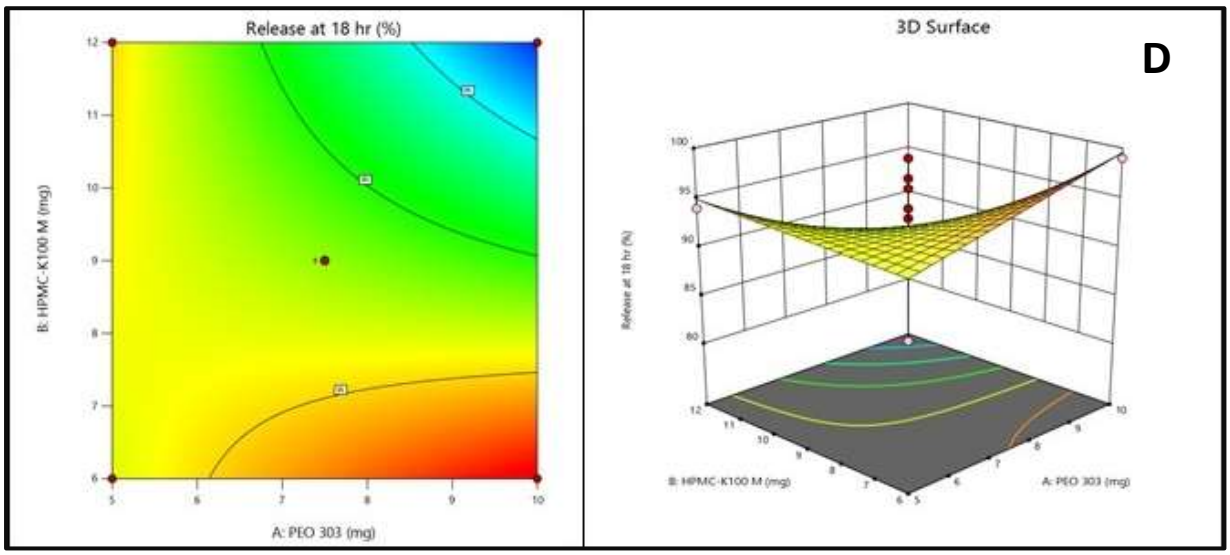
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **15** | **T15** | **Factorial** | 10 | 12 | 6 | 29 | 44 | 85 | 94 |
| **16** | **T16** | **Center** | 7.5 | 9 | 13 | 33 | 59 | 94 | 101 |

It was observed after all time point of release; the Model F-value implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise. At all response *p-values* foundto be less than 0.0500 indicate model terms are significant.




Release at 12hr (%)
B: HPMC-K100 M (mg)
A: PEO 303 (mg)
3D Surface
C
Release at 12hr (%)
B: HPMC-K100 M (mg)
A: PEO 303 (mg)


Release at 18 hr (%)
B: HPMC-K100 M (mg)
A: PEO 303 (mg)
3D Surface
D
Release at 18 hr (%)
B: HPMC-K100 M (mg)
A: PEO 303 (mg)

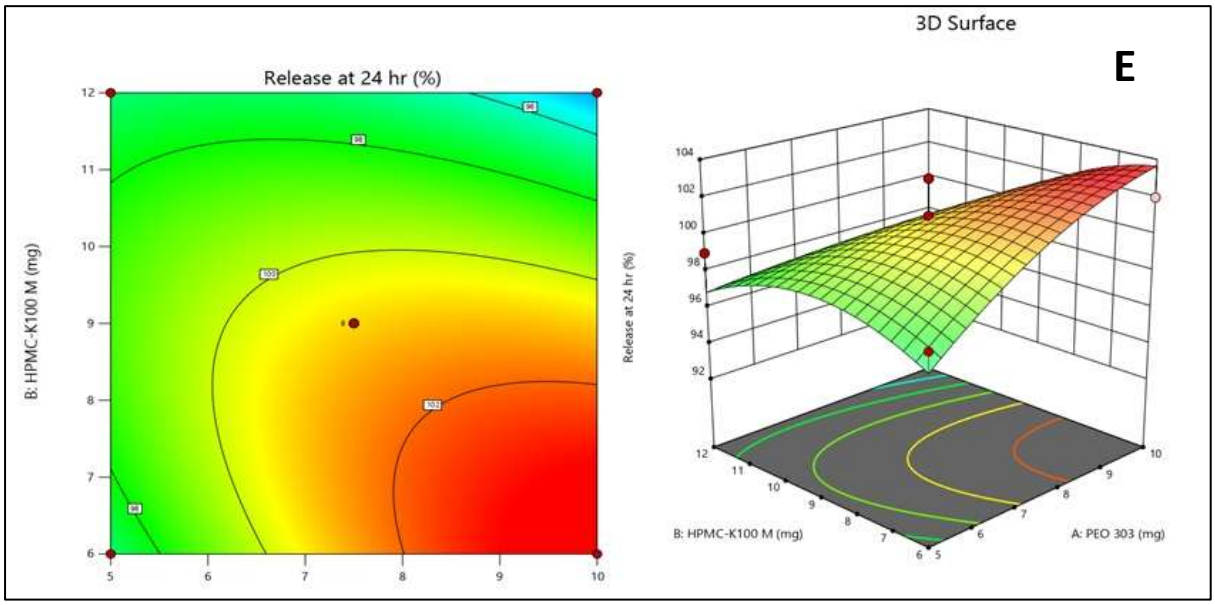



**Figure 2.Contour plots of response drug release; A. at 2hrs; B. at 6 hrs; C. at 12 hrs; D. at 18 hrs and E. at 24 hrs.**

The values of predicted $R^2$ were in reasonable agreement with the Adjusted $R^2$ i.e. the difference was less than 0.2. Adequate precision measures the signal to noise ratio. A ratio greater than 4 is desirable. This model can be used to navigate the design space. The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients are adjustments around that average based on the factor settings. In above figure, contour plots indicate that level of formulation variable have impact on the response factor at initial stage of release profile. Slow release was observed with high level & vice versa. Contour plot indicates that level of formulation variable have impact on the response factor at 12 hrs, at 18 hrs and at 24 hrs with curvature. Curvature was indicating the formulation have the characteristics of modified release profile. Level of polymeric variable design the pattern of curvature.

**Table 5. ANOVA table of CCD design**

| **Response** | **Intercept** | **A** | **B** | **AB** | **$A^2$** | **$B^2$** |
|---|---|---|---|---|---|---|
| **Release at 2 hr.** | 14.25 | 1.96599 | -6.33731 | | | |
| **p-values** | | 0.0577 | < 0.0001 | | | |
| **Release at 6 hr.** | 33.9375 | 1.46599 | -4.74632 | | | |
| **p-values** | | 0.0618 | < 0.0001 | | | |
| **Release at 12hr** | 57.6875 | 2.31066 | -7.5052 | -5 | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **p-values** | | 0.0856 | < 0.0001 | 0.0142 | | |
| **Release at 18 hr** | 92.25 | -2.0481 | -4.35876 | -5 | | |
| **p-values** | | 0.1986 | 0.0134 | 0.0368 | | |
| **Release at 24 hr** | 100.875 | 1.11244 | -2.28921 | -2.25 | -1.0625 | -1.8125 |
| **p-values** | | 0.1214 | 0.0059 | 0.0360 | 0.1370 | 0.0202 |

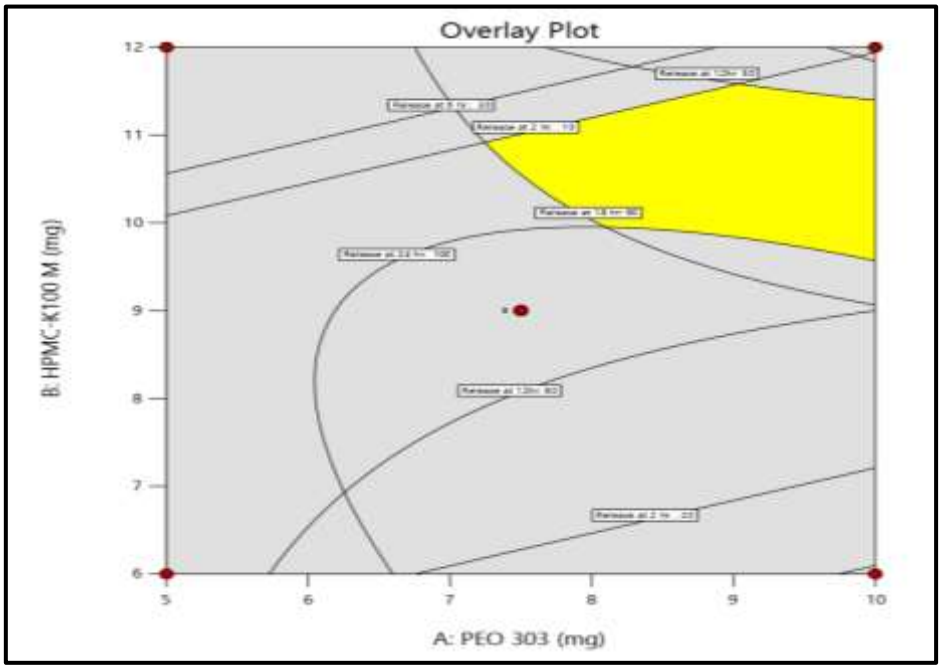



**Figure 3. Overlay spectra of Furosemidemucoadhesive tablets**

Based on the results obtained a cut off values of desire release an overlay plot was obtained. Based on the given design space three check point batches were prepared, their composition is shown in the Table. %Prediction error was found to be less than 5% in all prepared checkpoint batches which confirms the prediction power of the model suggested by software.

**Table 6 % PE response of CCD design**

| Response | Predicted Mean | Experimental Mean | %PE* |
|---|---|---|---|
| Release at 2 hr. | 13.0427 | 13.62 ±0.21 | -4.42623 |
| Release at 6 hr. | 33.0383 | 32.58±0.24 | 1.387178 |
| Release at 12hr | 56.0783 | 56.87±0.30 | -1.41178 |
| Release at 18 hr | 93.861 | 92.54±0.45 | 1.4074 |
| Release at 24 hr | 99.3981 | 99.21±0.59 | 0.189239 |

*** %PE=Percentage predicted error**

Optimized batches SD8 were also characterized for Average weight (59.40±1.26 mg), thickness (2.85±0.01 mm), Hardness (75.90±8.62 N) and *in vitro* release studies up to 24 hrs of all 16 runs as represented in following figure.

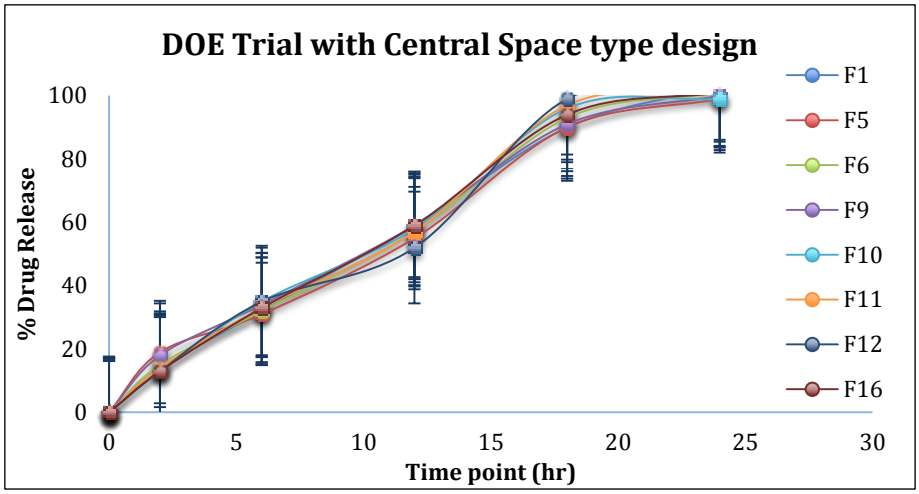



**Figure 4. Dissolution of DOE Trial with central space type design**

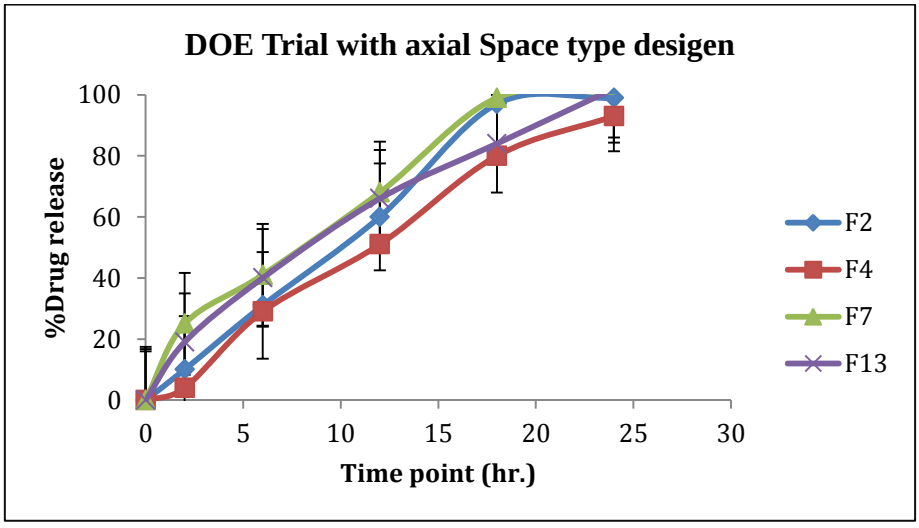



**Figure 5. Dissolution of DOE Trial with axial space type design**

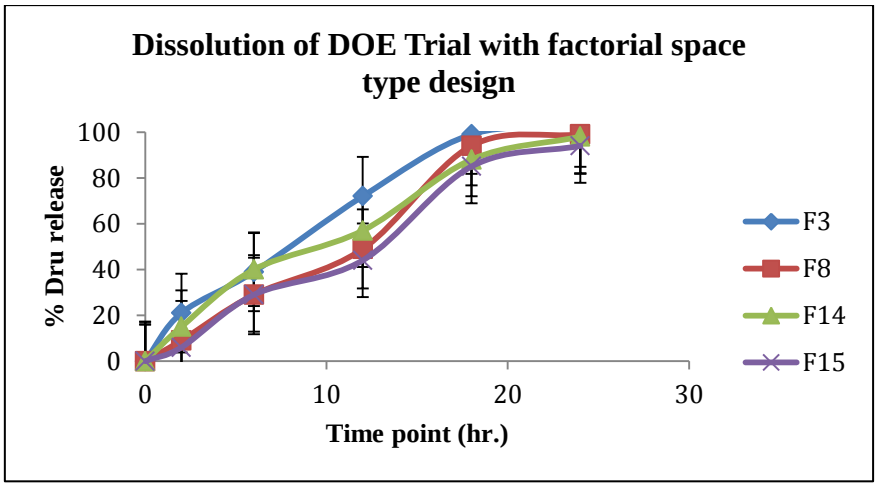



**Figure 6. Dissolution of DOE Trial with factorial space type design**

**Preparation of Solid dispersion of Furosamide**

Solid dispersions prepared using various drug:polymer ratio showed significant improvement in solubility of furosemide. Based on their solubility data (as shown in Table 7) all the solid dispersions were further incorporated in mucoadhesive minitablet formulation previously optimized using design of experiment technique.

**Table 7 Solubility data of different solid dispersion batches.**

| Sr. No | Drug :Polymer Ratio (PVP K30) | Solubility in water at $37^0$C* (µg/ml) | Drug :Polymer Ratio (PEG 6000) | Solubility in water at $37^0$C* (µg/ml) |
|---|---|---|---|---|
| 1. | Plain drug | 19.3 ± 0.7 | Plain drug | 19.3 ± 0.7 |
| 2. | 1:0.1 | 41.98 ± 2.1 | 1:0.1 | 41.2 ± 1.5 |
| 3. | 1:0.5 | 69.89 ± 4.3 | 1:0.5 | 66.95 ± 2.8 |
| 4. | 1:1 | 85.29 ± 6.2 | 1:1 | 81 ± 4.7 |

*Mean ± S.D.

Above phase solubility study indicates that polymer concentration has significant impact on the solubility of poorly soluble drug furosemide. However, increase in concentration of polymer also increase in solubility was observed for both the polymers.

**Incorporation of solid dispersion in mucoadhesive tablet**

All the 12 batches were evaluated for tablet parameters as well as *in vitro* dissolution studies. Following graph represents the drug release pattern of trial no.SD1 to SD12. Solubility studies of prepared solid dispersions clearly demonstrated that basic pH modulators can increase solubility of drug very significantly by increasing micro environmental pH.

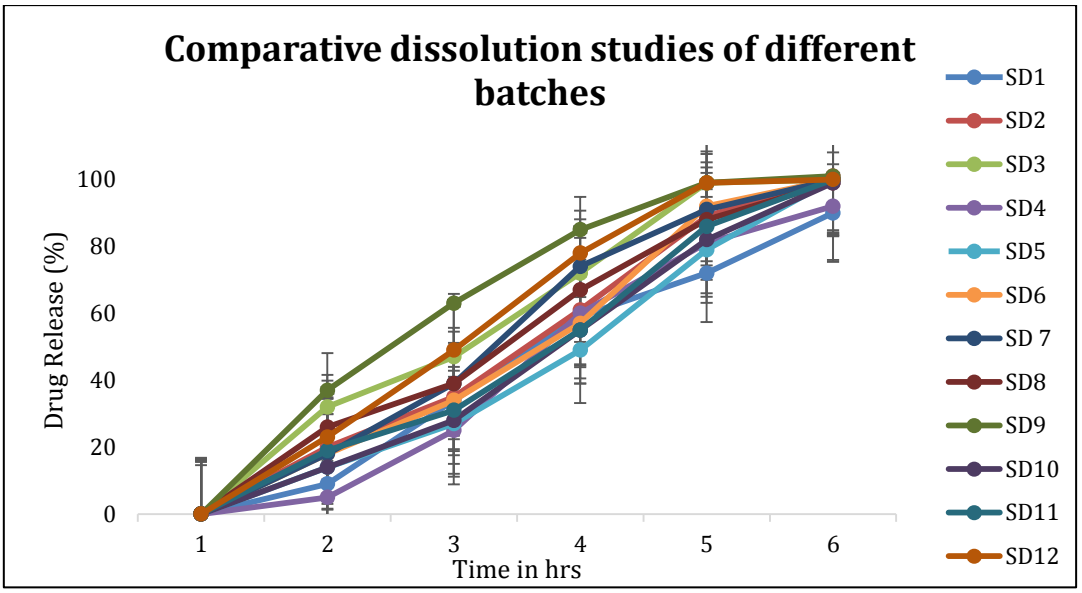



**Figure 7. Comparative dissolution of polymer along with pH modular**

Solid dispersion prepared by Drug: polymer ratio of 1:1 increased furosemide solubility in water upto 0.1 mg/ml. While in presence of basic pH modulator, above solid dispersion showed further significant increase in drug release when incorporated in mucoadhesive tablet formulation. Optimization formulationSD8 derived from the experimental design showed an extended release profile up to 24 hrs with sufficient adhesive strength to retain the dosage form in stomach. So based on the release studies batch SD8 showed desired release.

## 4. Conclusion

Furosemide is a weakly acidic BCS class IV drug molecule with low solubility. Hence mucoadhesive minitablet of furosemide equivalent to 5 mg has been designed using different polymers. Suitable polymer combination of PEO WSR 303 & HPMC K100M was identified with their levels by DoE trials. The outcome of Central Composite Design revealed that the both formulation variables PEO WSR 303 and HPMC K100 M have significant impact on the dependent response like dissolution at various time points like 2 hrs, 6 hrs, 12 hrs and 24 hrs. However, because of low solubility of Furosemide in acidic pH, drug could not be solubilized in the matrix form and hence can't come out of mucoadhesive formulation completely. Hence second strategy designed for solubility enhancement with solid dispersion with two polymers along with pH modulator (Sodium bicarbonate) for keeping matrix core in situ as basic pH to solve proximity to absorption window issue. Solid dispersion of PVP K 30, PEG 6000 equivalent to 5 mg Furosemide in combination to Sodium bicarbonate were added into the optimized composition of DoE & different trials were executed as SD1 to SD12. Solubility studies of prepared solid dispersions in combination to pH modulator clearly demonstrated that basic pH modulators can increase the solubility of drug very significantly by increasing in situ micro environmental pH. Solid dispersion prepared by Drug: PVP K-30 ratio of 1:1 increased Furosemide solubility in water about 5 times. Minitablet formulation SD8 containing solid dispersion and pH modulator demonstrated optimum drug release pattern. However, in present work, *in vitro* studies were found insufficient to prove the applied conception of releasing drug in the proximity of GI tract absorption surface to improve its

permeability. So here, we suggest further *in vivo* studies for optimized formulation and also propose to incorporate permeation enhancers in the formulation to get clear idea regarding the role of proximity and permeation enhancers.

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