MUCAODHESIVE EFFECT OF POLYETHYLENEOXIDE ON FAMOTIDINE NANOSUSPENSION PREPARED BY SOLVENT EVAPORATION METHOD

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ABSTRACT

Low oral bioavailability of poorly water-soluble drugs poses a great challenge during drug development. Poorly water-soluble compounds are difficult to develop as drug products using conventional formulation techniques and are frequently abandoned early in discovery. The aim of the present study was to improve the dissolution rate of a poorly water-soluble drug, famotidine, by a nanoprecipitation technique. To overcome the problem of the high elimination rate caused by nonsteroidal anti-inflammatory drug (NSAID) induce ulcer, famotidine was formulated as a mucoadhesive nanosuspension, i.e. combining the properties of mucoadhesive drug delivery systems, with nanosuspensions. In this study polyethylene oxide (PEO) as mucoadhesive polymer were employed to create a prolonged retention time for the FAM loaded nanosuspension. Formulations evaluated for particle size determination, viscosity, mucoadhesion study, and in vitro drug release study. PEO grades and their concentration were effect on retention of nanosuspension and controlled the drug release for longer period. It may be concluded that formulation (M3) with a composition of 1.6% WSR N-60k, was selected as the final optimized formulation that exhibited pseudoplastic behaviour, and maximum mucoadhesive strength. The optimized formulation was shown 29.00% for percent drug released within 1 hr (Q1), 94.79% for percent drug released within 8 hr (Q2) and 104.03 for mean dissolution time (MDT).

Keywords: Mucoadhesive Nanosuspension, Famotidine, Polyethylene Oxide

INTRODUCTION

Oral administration is the most convenient, widely utilized, and preferred route of drug delivery for systemic action. The solubility/dissolution behavior of a drug is key determinant to its oral bioavailability. An improvement of oral bioavailability of poor water-soluble drugs remains one of the most challenging aspects of drug development.2,3 Famotidine (FAM) is a histamine H2-receptor antagonist. It is widely prescribed in gastric ulcers, duodenal ulcers, Zollinger-Ellison syndrome and gastro esophageal reflux disease. The incomplete and variable bioavailability of famotidine has been attributed to its poor aqueous solubility (Class IV). In spite of the great therapeutic interest of this drug, the bioavailability after oral dosing is low (20–40%) with a higher variability.4 In recent years, much attention has been focused on drug nanosuspensions for the bioavailability improvement of water insoluble drugs. However, the poor solubility is not the only problem associated with FAM for the treatment of NSAID induces ulcers. Conventional dose of 20 mg can inhibit gastric acid secretion up to 5 hours but not up to 8-10 hours. An alternative dose of 40 mg leads to plasma fluctuations and NSAID induce ulcers leads to severe mucosal damage which increasing the passage velocity of the administered drug in the stomach. The use of mucoadhesive drug delivery systems for systemic or local delivery of various drugs has attracted a great deal of attention in recent years.

A preparation that spreads out, adheres to the gastric mucosal surface, and continuously releases drug that should be highly effective against NSAID induce ulcers like aspirin. When formulating a successful drug delivery system, numerous formulations related parameters should be taken into account. Regarding the mucoadhesive drug delivery systems, studies have been conducted on the effect of various formulation additives on the adhesive-ability of mucoadhesive polymers and formulations. Hence an attempt was made in this current study to combine the nanosuspension technology to improving aqueous solubility of FAM and polyethylene oxide (PEO) as mucoadhesive polymer to retain nanosuspension for systemic as well as local delivery of FAM, which would efficiently reduce gastric acid secretion.

MATERIALS AND METHODS

MATERIALS

Famotidine was obtained as a gift sample from Cadila Pharmaceutical Ltd., Ahmedabad, India. Lutrol F-68 (Poloxamer-188) was obtained as a gift sample from Torrent Pharmaceutical Ltd. Methanol was obtained as a gift sample from S.D.Fine Chemicals Ltd., Mumbai, India. Polyethylene oxides (WSR N-60k, WSR‐301 and WSR‐303) were obtained as a gift sample from Colorcon Asia Ltd, Goa, India.

METHODS

Preparation of mucoadhesive nanosuspensions

Nanosuspensions were prepared by the solvent evaporation technique. Famotidine was dissolved in a methanol (6 ml) at room temperature. This was poured into 10 ml water containing 25mg of Lutrol F-68 maintained at a temperature of 30–40°C and subsequently stirred at1200 rpm for 1 hr to allow the volatile solvent to evaporate (Remi, High speed stirrer, India.). Addition of organic solvent by means of a syringe positioned with the needle directly into surfactant containing water. Organic solvents were left to evaporate off under a slow magnetic stirring of the nanosuspensions at room temperature for 2 hours. For preparation of mucoadhesive nanosuspension, WSR N-60k, WSR-301 and WSR-303 (1.2%, 1.4%, 1.6% w/v) were dispersed in bidistilled water with slow magnetic stirring (Remi, India) left to equilibrate for 24 hrs. Different concentrations of polymer solutions were incorporated into the previously prepared nanosuspension. The combination was strongly mixed by high speed magnetic stirring during the incorporation of polymer solutions (Table 1).

Particle size and its morphology

The particle size of the produced nanosuspension was analyzed by photon correlation spectroscopy (PCS) using a Zetasizer 5000 (Malvern Instruments Ltd., UK). Sample was measured appropriately after diluted with bidistilled water. The nanoparticle surface appearance and shape were analyzed by scanning electron microscopy (SEM).

Determination of famotidine solubility

The solubility of FAM in water, methanol, ethyl acetate and nanosuspension were determined. According to the obtained results, the best solubility of FAM was obtained with nanosuspension. The suspensions were stirred on a magnetic stirrer at 25°C for 24 h, filtered (0.22 μm). Content of dissolved famotidine was analyzed by UV method at 267nm (Systronic 2203, Japan).
Rheological measurements

The viscosity of mucoadhesive nanosuspension was determined by Brookfield viscometer. Take the test sample in a clean and dry 25 ml test tube. Determine the viscosity of the test sample as per standard operating procedure of viscometer by using spindle no 3.Use the spindle for finding out the viscosity of the sample at speeds of 6, 12, 30 and 60 r.p.m. respectively. Record the dial reading and calculate the viscosity of test sample. The dial readings were repeated for three times.

In vitro mucoadhesive study

The method is based on the measurement of shear stress required to break the adhesive bond between a model membrane and the test formulation. The test formulation is sandwiched between two model membranes fixed on flexible supports in the assemblies for a sufficient period of time. After the adhesive bond has formed, the force (weight) required to separate the bond was measured and calculated as mucoadhesive strength (fig. 1).

In vitro drug release profile

FAM release from mucoadhesive nanosuspension was taken in modified diffusion cell apparatus (fig. 2). The drug release was determined using a dialysis tube (donor compartment) containing the known quantity (10 ml) of the mucoadhesive nanosuspension in a water-jacketed beaker containing 300 ml of 0.1N HCl (pH 1.2) at 37 ± 1°C for 8 hrs. The contents of the beaker were agitated at a magnetic stirrer. Samples were withdrawn periodically and replaced with an equal volume of fresh 0.1N HCl (pH 1.2). Samples were diluted suitably and filtered through a filter paper (0.22 µm). FAM content was determined by UV method at 267nm (Systronic 2203, Japan).

Drug Release Kinetics

Different kinetic models such as zero order (cumulative amount of drug released vs. time), first order (log cumulative percentage of drug remaining vs. time) and Higuchi model (cumulative percentage of drug released vs. square root of time) were applied to interpret the drug release kinetics from the mucoadhesive nanosuspension formulations. Based on the highest regression values (r²) for correlation coefficients for formulations, the best-fit model was decided. In order to authenticate the release model, dissolution data can further be analyzed by Poppaś and Korsmeyer’s equation.

\[ \frac{M_t}{M_\infty} = k_v t^n \]  

Where, \( \frac{M_t}{M_\infty} \) is the fraction of drug released at time \( t \), \( k \) is a constant and \( n \) characterizes the mechanism of drug release from the formulations during dissolution process. Value of \( n < 0.5 \) indicates case I (Fickian) diffusion or square root of time kinetics, \( 0.5 < n < 1 \) anomalous (non-Fickian) diffusion, \( n = 1 \) Case-II transport and \( n > 1 \) Super Case-II transport.

RESULTS AND DISCUSSION

Mucoadhesives have been a technology of great interest to pharmaceutical formulators and drug delivery scientists for many years. Adhesion refers to the relationship between two bodies, an adhesive and a substrate (both existing as condensed phases), when they are held together for an extended period of time by interfacial forces. Polyethylene oxides (WSR N-60k, WSR-301 and WSR-303) are useful in a wide variety of applications, particularly in pharmaceutical compositions. PEO can provide prolonged and improved coating and protection of stomach to inhibit irritation and accelerate healing of inflamed or damaged tissue. Furthermore, sustained or prolonged coating provides a matrix to deliver therapeutic agents to mucosal tissues at higher concentrations for higher efficacy, lower side effects, and sustained release of the active agent. Preparation of mucoadhesive nanosuspension in the classical way requires a three step production process, which means producing the nanosuspension, producing the different grades and amount of PEO solutions and finally mixing the two components. When nanosuspension was incorporated into PEO solutions, the caking problem was circumvented and systems were become physically stable.

For production of FAM nanosuspension, solvent evaporation with homogenization has been employed. Solvent evaporation method presents numerous advantages, in that it is a straightforward technique, rapid and easy to perform. Preliminary experiments were performed on amount of stabilizer, and stirring speed which were effective on the formation of nanosuspension. Amount of organic solvent was kept constant for all batches (table 1). Particle size distribution of FAM nanosuspension at 25mg of Lutrol F-68 and 1200 rpm of stirring speed was 470.5nm with 0.120 µm. Dispersity index (fig. 3 and 4).

Table 1: Formulation of famotidine mucoadhesive nanosuspensions

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>( M_1 )</th>
<th>( M_2 )</th>
<th>( M_3 )</th>
<th>( M_4 )</th>
<th>( M_5 )</th>
<th>( M_6 )</th>
<th>( M_7 )</th>
<th>( M_8 )</th>
<th>( M_9 )</th>
<th>( M_{10} )</th>
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<tr>
<td>Famotidine (mg)</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Methanol (ml)</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
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</tr>
<tr>
<td>WSR N-60k (% w/v)</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
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<tr>
<td>WSR 301 (% w/v)</td>
<td>1.2</td>
<td>1.4</td>
<td>1.6</td>
<td>1.2</td>
<td>1.4</td>
<td>1.6</td>
<td>1.2</td>
<td>1.4</td>
<td>1.6</td>
<td></td>
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<tr>
<td>Volume of aqueous solvent</td>
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<td>1200</td>
<td>1200</td>
<td>1200</td>
<td>1200</td>
<td>1200</td>
<td>1200</td>
<td>1200</td>
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<td>Stirring Speed (Rpm)</td>
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<td>1200</td>
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<td>1200</td>
<td>1200</td>
<td>1200</td>
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Rheological measurements of mucoadhesive nanosuspension

The main prerequisite of mucoadhesive nanosuspension is its rheological behaviour. For most liquids, viscosity remains constant over a wide range of shear rates. This phenomenon is known as newtonian viscosity, and liquids which display this property are called newtonian liquids. Liquids in which viscosity varies with shear rate are termed non-newtonian. There are several known non-newtonian profiles. One of these profiles is termed pseudoplastic, and liquids which fall into this category demonstrate a decrease in viscosity as shear rate increases. Preferred formulations of the current invention are pseudoplastic, and demonstrate a decrease in viscosity at low shear rates. Pseudoplasticity benefits the application of the formulations of the current invention by virtue of the fact that application of shear (for example, swishing the liquid in the mouth) reduces the viscosity, so allowing the liquid to flow and coat the mucosal surface more readily. Once the shear forces are discontinued, the
viscosity of the liquid increases, as required (in combination with mucoadhesion) for prolonged attachment to the mucosal surface.6

Table 2: Solubility of famotidine

<table>
<thead>
<tr>
<th>Famotidine solubility (mg/10ml)</th>
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<tbody>
<tr>
<td>Nanosuspension</td>
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<tr>
<td>Methanol</td>
</tr>
<tr>
<td>Ethyl acetate</td>
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<tr>
<td>Water</td>
</tr>
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Table 3: Viscosity profile of mucoadhesive nanosuspension

<table>
<thead>
<tr>
<th>RPM</th>
<th>M1</th>
<th>M2</th>
<th>M3</th>
<th>M4</th>
<th>M5</th>
<th>M6</th>
<th>M7</th>
<th>M8</th>
<th>M9</th>
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<tr>
<td>6</td>
<td>200</td>
<td>200</td>
<td>236</td>
<td>300</td>
<td>450</td>
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<td>3600</td>
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<td>12</td>
<td>100</td>
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<td>10</td>
<td>60</td>
<td>190</td>
<td>130</td>
<td>200</td>
<td>200</td>
<td>400</td>
<td>640</td>
<td>1020</td>
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</table>

Table 4: Q1, Q8 and MDT for nanosuspension with PEO and without PEO

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>M1</th>
<th>M2</th>
<th>M3</th>
<th>M4</th>
<th>M5</th>
<th>M6</th>
<th>M7</th>
<th>M8</th>
<th>M9</th>
<th>M15*</th>
</tr>
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<tbody>
<tr>
<td>Q1</td>
<td>25.03</td>
<td>28.70</td>
<td>29.00</td>
<td>35.73</td>
<td>43.29</td>
<td>44.35</td>
<td>34.88</td>
<td>40.64</td>
<td>35.94</td>
<td>49.92</td>
</tr>
<tr>
<td>Q8</td>
<td>95.37</td>
<td>95.10</td>
<td>94.79</td>
<td>99.32</td>
<td>98.95</td>
<td>99.84</td>
<td>96.85</td>
<td>98.71</td>
<td>97.88</td>
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<tr>
<td>MDT</td>
<td>100.96</td>
<td>103.48</td>
<td>104.48</td>
<td>66.07</td>
<td>77.43</td>
<td>96.83</td>
<td>92.31</td>
<td>93.52</td>
<td>95.23</td>
<td>28.07</td>
</tr>
</tbody>
</table>

*Formulation M10 was not contained PEO as mucoadhesive polymer

Table 5: Diffusion exponent (n) of peppas model and regression coefficient (r2) of mucoadhesive nanosuspension according to different kinetic models

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>M1</th>
<th>M2</th>
<th>M3</th>
<th>M4</th>
<th>M5</th>
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<tr>
<td>n</td>
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<td>0.9996</td>
<td>0.9996</td>
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<td>0.9996</td>
<td>0.9979</td>
<td>0.9573</td>
<td>0.9983</td>
<td>0.9975</td>
<td>0.9934</td>
</tr>
<tr>
<td>r2</td>
<td>0.9902</td>
<td>0.9904</td>
<td>0.9936</td>
<td>0.9911</td>
<td>0.9477</td>
<td>0.9121</td>
<td>0.9869</td>
<td>0.9983</td>
<td>0.9862</td>
<td>0.9484</td>
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<tr>
<td>n</td>
<td>0.9542</td>
<td>0.9583</td>
<td>0.9645</td>
<td>0.9645</td>
<td>0.9115</td>
<td>0.8799</td>
<td>0.9482</td>
<td>0.9671</td>
<td>0.9484</td>
<td>0.499</td>
</tr>
<tr>
<td>r2</td>
<td>0.6381</td>
<td>0.5778</td>
<td>0.5790</td>
<td>0.4925</td>
<td>0.3941</td>
<td>0.3863</td>
<td>0.5295</td>
<td>0.4267</td>
<td>0.499</td>
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</table>

In vitro mucoadhesion study

Mucoadhesion is desirable characteristics of a nanoparticulate dosage form. The present invention involves a finding that neither high viscosity nor mucoadhesion alone confers ideal properties. A viscous but non-mucoadhesive liquid will not be held in place on the mucosal surface. Instead, a non-mucoadhesive solution will readily be lost from the point of application, for example, under the influence of gravity, and/or through natural movements of the membrane and surrounding structures, and/or through the flow of natural secretions. In a mucoadhesive, viscous liquid formulation, the liquid will adhere to the mucosa, while the high viscosity of the liquid will reduce the rate of removal of the bulk of the liquid from the site of application. PEO is act as mucoadhesive agent may itself be a viscosity-inducer and thus serve two purposes.

Performed shear stress studies prove the mucoadhesive nature of PEO. As same in viscosity, PEO grades as well as their concentration were affected on mucoadhesion. PEO grades are important parameter that enhances the mucoadhesive property of FAM loaded nanosuspension.

The present invention involves WSR N-60k, WSR-301 and WSR-303 as PEO grades. The mucoadhesion was significantly affected by the polymer molecular weight characteristics. The in vitro test data indicated that maximum adhesion occurred at an average molecular weight of 2,000,000 and a further increase in molecular weight caused a decrease in adhesion (fig. 5).

The effect of different concentrations of PEO on mucoadhesion force is shown in figure 4. The mucoadhesion force was significantly increased as the concentration of mucoadhesive polymer increased in the range of 1.2-1.6 %. Formulation M1-M3 using 1.2-1.6 % of WSR N-60k exhibited maximum mucoadhesive strength. This also proved that WSR N-60k has better mucoadhesive property than WSR-301 and WSR-303, even though, they showed higher viscosity. The results indicated that molecular weight of PEO grades and their concentration significantly affect on mucoadhesive property of nanosuspension.

In vitro drug release study

The in vitro drug release profile of FAM from the mucoadhesive nanosuspension containing different grades and amount of PEO is shown in fig. 6. Drug release studies of famotidine nanosuspension (M1-M15) and all other prepared mucoadhesive nanosuspension (M1-M15) were carried out in 0.1N HCl (pH 1.2). Q1 (percent drug released within 1 hr), Q8 (percent drug released within 8 hr), and mean dissolution time (MDT) values calculated from release profile are reported in Table 4.
Fig. 1: Shear stress measurement method

Fig. 2: Schematic representation of modified diffusion cell apparatus

Fig. 3: Particle size distribution of optimized nanosuspension at Lutrol F-68; 25mg Stirring speed; 1200 rpm

Fig. 4: Scanning electron microscopy of optimized nanosuspension at Lutrol F-68; 25mg, stirring speed; 1200 rpm
All 3 PEO grade mucoadhesive formulations, M1-M9, appear to control the release of FAM, but with a varying degree. Dissolved drug diffuses out of the PEO network at a rate determined by the amount and viscosity of PEO in the nanosuspension formulation. All the formulations, M1-M9, showed a biphasic release profile. There was a faster drug release from 0 to 1 hour, followed by a slower release from 2 to 8 hours. Such a biphasic release pattern may be beneficial in providing the initial therapeutically effective plasma concentration followed by an extended plasma concentration. This biphasic pattern of release is a characteristic feature of matrix diffusion kinetics. The drug release profiles were characterized by an initial burst effect (more than 20% drug release in first hour and slow release thereafter). The biphasic release is often observed from hydrophilic matrix systems. As the release-rate-limiting polymer changes from a glassy state to a rubbery state, a gel structure is formed, which considerably decreases the release of the drug since the drug has to diffuse through this gel barrier into the bulk phase. The strength of the gel depends on the chemical structure and molecular size of the polymer.

Fig. 5: In vitro mucoadhesion profile of famotidine mucoadhesive nanosuspension formulations.

Dissolution of famotidine nanoparticles were affected by different PEO grades and their concentrations. The formulation M1, M2, and M3 containing low molecular weight and viscosity grade of PEO, WSR N-60k (1.2, 1.4 and 1.6%) showed the 25.60% , 28.70% , 29.00% for Q1 and 95.37%, 95.10%, 94.79% for Q8 consequently.

The formulations M4 to M9 might be contributing their tough control of drug release owing to the higher viscosity of WSR-301 and WSR-303. It is known that higher viscosity grade polymer (WSR-303) hydrates at a faster rate and, therefore, it is capable of forming a gel structure faster than a medium viscosity grade (WSR-301) and low viscosity grade (WSR N-60k) polymer. It is expected that higher viscosity PEOs are ideal candidates in providing a controlled release. But in the present study, low-viscosity PEO grade (WSR N-60k) was able to provide controlled drug release as that of medium- and high-viscosity grade PEOs (WSR-301 and WSR-303). In the formulations M4-M9, more than 30% drug release within 1 hours and more than 90% drug release up to 8hrs.

MDT reflects the time for the drug to dissolve and is the first statistical moment for the cumulative dissolution process that provides an accurate drug release rate.1 It is accurate expression for drug release rate. A higher MDT value indicates greater drug retarding ability.14 MDT values were calculated using equation

\[ \text{MDT}_{\text{in vitro}} = \frac{\sum t_{\text{mid}} \Delta M}{\sum \Delta M} \]  

(2)

Here, \( i \) is dissolution sample number, \( n \) is number of dissolution times, \( t_{\text{mid}} \) is time at the midpoint between times \( t_i \) and \( t_{i-1} \), and \( \Delta M \) is the amount of famotidine dissolved (μg) between times \( t_i \) and \( t_{i-1} \).

MDT value of pure famotidine nanosuspension (\( M_{\text{pol}} \)) is low (28.07 min). This value increased to a greater extent after preparing its mucoadhesive nanosuspensions using PEO. M3 showed highest MDT value (104.48 min). MDT values of batch M3 were higher than other prepared mucoadhesive nanosuspension. This was proved that WSR N-60k has better drug retarding ability than WSR-301 and WSR-303, even though; they showed higher viscosity and molecular weight.

Fig. 6: In vitro drug release profile of famotidine mucoadhesive nanosuspension formulations.
Drug release kinetic

The zero-order rate describes systems where drug release is independent of its concentration and is generally seen for poorly water soluble drug in matrix, transdermals, etc. The first-order rate describes systems in which the release is dependent on its concentration (generally seen for water-soluble drugs in porous matrix). The Higuchi model describes the release of the drug from an insoluble matrix to be linearly related to the square root of time and is based on Fickian diffusion. The data is shown in Table 5.

When the drug release data was treated with different models, it was observed that neither of the formulations followed the first order or zero order release kinetics. Release of the drug from the mucoadhesive nanosuspension generally follows the diffusion pattern where the drug is being transported from the dosage matrix into the receptor media depending on the concentration. As concentration gradient varies, the drug is released, and the distance for diffusion increases. The in vitro release profiles of both the drugs from all the formulations could be best expressed by Higuchi’s equation. The plots showed highest linearity with r² values ranging from 0.9573-0.9996. The ‘n’ values for M1 to M3, which is less than 1 and greater than 0.5 follows Non Fickian diffusion mechanism. Table 5 showed that M4-M9 the formulations release the drug by diffusion following Fickian (n<0.5) transport mechanism except the formulation M0, which follow non-Fickian (n>0.5) transport mechanism.

CONCLUSION

The famotidine loaded mucoadhesive nanosuspension was prepared containing PEOs grades in with varying concentration to obtain the therapeutic effects over a period of 8 hours. A series of experiments have been carried out which indicated that the presence of PEOs as mucoadhesive polymer can affect the viscosity, mucoadhesion and in vitro drug release up to 8hrs. The process of in vitro release profile was optimized with respect to the parameters like the Q₁ (percent drug released within 1 hr), Q₈ (percent drug released within 8 hr), and mean dissolution time (MDT). Performed studies and obtained results prove the efficacy of PEOs based FAM mucoadhesive nanosuspension system for NSAID induced ulcer treatment.

REFERENCES