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Formulation and Evaluation of Sustained Release Matrix Tablets of Furosemide Using Different Polymers

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ABSTRACT

Objective: The aim of the present research study was to develop and evaluate sustained release matrix tablets of 100 mg furosemide using direct compression method.

Method: Eighteen formulations were prepared using different natural polymers including xanthan gum, bees wax, carnauba wax and synthetic polymers i.e. HPMC (K100M, K15M, and K4M). These all polymers were used in different proportion to control the released of the drug. All formulations were evaluated using micromeritics studies of powder blend and different physicochemical tests.

Results: All the physicochemical characters of the formulated tablets were within acceptable limits. The release pattern of the drug was observed over a period of 12 hours and determined the amount of drug by the UV-Visible spectroscopic method. Dissolution data showed that the formulated tablets with Xanthan gum and hydroxyl propyl methylcellulose (HPMC) provided sustained release of the drug up to 12 hrs. Most of the formulations containing these two polymers were followed zero-order kinetics, Korsmeyer-Peppas and Higuchi models.

Conclusion: Hence economically it may be suitable for the pharmaceutical industries to use this type of simple technologies for the development of advanced formulations. Therefore, we conclude that the objective of this study was to formulate a sustained release matrix dosage form of furosemide using different polymers and their different proportions have been achieved.

Keywords: Direct compression, furosemide, natural polymers, synthetic polymers, sustained release tablets.

INTRODUCTION

Furosemide is indicated in pulmonary edema as well as in cardiac and hepatic edema. The drug is also used in hypertension and in the treatment of cardiac infarction. The drug acts on ascending limb of the loop of Henle in the kidney and provide diuretic action [1]. A perfect drug delivery system is that which is able to deliver the desired therapeutic amount of drug for a longer period of time. Most drugs do not stay long in the body due to their short half-life and then its multiple dosing is required for therapeutic outcome. To resolve the multiple dosing problems, sustained release drug delivery systems have been focused. Different drug deliveries technologies are used to modify drug release pattern which ultimately increases the retention time of drug and patient compliance [2]. Drug released from the dosage form by different mechanisms including diffusion, degradation, swelling, and affinity-based mechanisms. Preferred routes for administration of the drug are the non-invasive

methods i.e. peroral, topical, transmucosal and inhalational [3].

Sustain release dosage forms are easily manufactured using matrix system of different control release excipients. Usually, insoluble gum and waxes are used (for extending the release of drugs) as matrix-forming components. Waxes have an advantage over other materials because it is chemically inert against other materials. The waxy and hydrophobic materials are easily erodible and well control the release pattern of the drug through the mechanism of erosion and pore diffusion. Many researchers used carnauba wax as deterrent material in different sustained released formulations [4,5]. Xanthan gum is among the most popular hydrophilic natural polymer because of their cost-effectiveness and regulatory acceptance. Moreover, it is a high molecular weight hydrophilic polymer used as a suspending agent, thickening agent and emulsifying agent. The hydrophilic polymers develop a viscous gelatinous surface barrier after hydration; this gelatinous barrier controls the drug release from matrix systems [6]. In hydrophilic controlled release matrix system, HPMC is commonly used. It is available in a wide range of molecular weights and it effectively controls its gel viscosity. Many formulators used HPMC for the formulation of hydrophilic matrix system because of its strong and viscous gel formation to controls the release of drugs [7,8].

Furosemide is mainly absorbed from stomach or upper GI tract, due to its weak acidic nature (pKa 3.8). This narrow pathway for absorption is responsible for its variable absorption and low bioavailability when given orally [9]. It is also reported in previous studied that furosemide have poorer oral bioavailability of about 37–51% [10]. These all reasons together form a base for formulating a modified release dosage form of furosemide. Such a formulation, which will be retain for longer period of time in upper GI to liberate and absorb drug in control and sustain manner.

Moreover, immediately release formulations of furosemide cause maximum diuresis in a shorter time period which is inconvenient and irritable especially for geriatric patients [11]. In contrast, sustained drug release matrix system is a novel drug delivery system that can be used as an alternative to immediate drug delivery system. These sustained released systems produce control diuresis effects which are well tolerated and convenient for patients. It increases patient adherence, avoid multiple dosing and reduce side effects and other problems related to immediate drug delivery systems. Therefore, the aim of current study was to assess the strength of xanthan gum, carnauba wax, beeswax and HPMC (K4M, K15M, and K100M) on sustaining the release of furosemide from the matrix system. Furthermore, the influence of different polymers nature and concentration was evaluated on the release pattern of furosemide.

Table 1. Sustained release formulations with combined natural and synthetic matrix materials.

S.No	Batch Code	Drug: Polymer Ratios	Xanthan Gum	Bees wax	Carnauba wax	HPMC (K4M)	HPMC (K15M)	HPMC (K100M)	Total weight of tablet
1	F1	1:1	100	--	--	--	--	--	306
2	F2	1:2	200	--	--	--	--	--	406
3	F3	1:3	300	--	--	--	--	--	506
4	F4	1:1	--	100	--	--	--	--	306
5	F5	1:2	--	200	--	--	--	--	406
6	F6	1:3	--	300	--	--	--	--	506
7	F7	1:1	--	--	100	--	--	--	306
8	F8	1:2	--	--	200	--	--	--	406
9	F9	1:3	--	--	300	--	--	--	506
10	F10	1:1	--	--	--	100	--	--	306
11	F11	1:2	--	--	--	200	--	--	406
12	F12	1:3	--	--	--	300	--	--	506
13	F13	1:1	--	--	--	--	100	--	306
14	F14	1:2	--	--	--	--	200	--	406
15	F15	1:3	--	--	--	--	300	--	506
16	F16	1:1	--	--	--	--	--	100	306
17	F17	1:2	--	--	--		--	200	406
18	F18	1:3	--	--	--		--	300	506

METHODOLOGY

Furosemide was procured from Sanofi-Aventis Pakistan Limited. Different grades of HPMC such as K100M, K15M, K4M were purchased from Nice Chemicals Pvt. Limited. Xanthan gum was obtained from Reforma-Italia Srl (Italy). Lactose DC kindly provided from Merck (Germany). Carnauba wax and bees wax were procured from Sigma-Aldrich (USA), talc, and magnesium stearate was received from Merck (Germany). All other chemicals used in this study were good pharmaceutical grades.

Apparatus & Equipment's

A UV-VIS Spectrophotometer (Model # UV-2700; Shimadzu, Kyoto, Japan). Dissolution Apparatus (paddle type) (Model # DT 126, Erweka, Germany). Mechanical sieve shaker (Model # 200CL, Octagon, UK), Single Punch Tablet Press machine (Tabletop Model, Mumbai, India), Tray dryer (Model # TD-12; India), Friability test apparatus (Model # TA3R, Erweka, Germany), hardness tester (Model # TBH 125, Erweka Germany). Vernier Caliper (Mitutoyo, Japan).

Preparation of Sustained Released (SR) Tablets

Sustained release tablets of furosemide were prepared using natural gummy and waxy materials (Xanthan gum, carnauba wax, bees wax) and synthetic polymers (Different grades of HPMC; K100M, K15M, K4M). This controlled release natural and synthetic materials were used in different ratios with the drug i.e. 1:1, 1:2 and 1:3, while the amount of the furosemide was kept constant as 100 mg. Lactose DC, talc and magnesium stearate were used as filler, lubricant and anti-adherent respectively. The composition of different formulations of sustained release matrix tablets is presented in Table **1**. All the ingredients were reduced and uniform their particle size by passing through # 100 sieves size then accurately weighed individually and mixed in a mortar with pestle using geometrical dilution method. The powder mixture was then compressed by single punch tablet press machine.

Micromeritics Properties of Powder Blends

Flow properties of obtained blends were evaluated using different micrometric tests i.e., bulk and tapped densities, Hausner's ratio, Carr's index, and the angle of repose. The obtained results are given with official limits of United States Pharmacopeia (USP) for the angle of repose.

Physical Evaluation of Tablets

Physical parameters including diameter, hardness, thickness, weight variation and friability were tested using official pharmacopoeial methods [11]. Ten tablets from each formulated batch were selected randomly for determination of thickness and diameter using digital Vernier caliper and the results of thickness and diameter of each tablet are reported in millimeters. Weight variation of 20 tablets was performed according to the official method of USP using digital balance and results of variability in weight of each formulation are given in milligrams. Six tablets of each formulation were taken and determined friability and hardness of each formulation using friability test apparatus and hardness tester respectively. The obtained results of friability were recorded in percentage and hardness results in kilograms.

Drug Content

The drug content of furosemide in each formulation was determined according to the modified method of Das et al used for the formulation study of furosemide [12]. Ten tablets from each formulation were randomly chosen, crushed separately and then taken powder equivalent to 100 mg into three 250 mL volumetric flasks. Add 250 mL of 0.1 N NaOH to each flask and sonicated for 30 mins. Then 1 mL solution was withdrawn from stock solution and diluted with 0.1 N NaOH up to 100 mL. The prepared solution was filtered using Whatman filter paper having 0.45 µm pore size. The filtrate absorbance was measured at 274 nm after filtering the solution and making suitable dilutions, using UV/Vis spectrophotometer. The drug content was determined according to the formula given in equation 1 using recorded absorbance of each sample.

$$\text{Drug content} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

Eq. 1

In-Vitro Drug Release Profile

The dissolution assessment was performed to evaluate the amount of furosemide released from

formulated matrix tablets using dissolution USP type II (paddle method) apparatus. Dissolution rate was determined using 900 mL of 0.1 N HCl for starting 2 hrs and then placed in phosphate buffer (pH 6.8) for complete release profile of furosemide. Six tablets of each batch were placed in each bowl of dissolution apparatus. The temperature of 37 ± 0.5 ^{o}C was maintained during the test and the paddle speed was fixed at 50 rpm. The samples of 10 mL were collected at different time intervals and were replaced with the same volume of fresh dissolution medium after each withdrawal. The collected filtrate was filtered using Whatman filter paper (0.45 µm pore size). Each sample was evaluated for drug contents by measuring absorbance at 274 nm using UV/Vis spectrophotometer [12].

Kinetics Models Studies

Several drug release kinetic models have been reported to evaluate the mechanism and pattern of drug release from immediate and modified release formulations [13]. Different kinetic models such as zero order model was applied on six best sustained release formulations to assess the released pattern of furosemide from matrix tablets, while Higuchi, Peppas–Korsmeyer and Hixon–Crowell equations were used to evaluate the mechanism of drug release followed by matrix tablets. Moreover, regression analysis was carried out and determined the best fit model by calculating the value of correlation factors using DD-Solver add-in program for Microsoft Excel.

Statistical Analysis

The all physicochemical evaluations test was carried out in triplicates. All obtained outcomes of quality evaluation tests were reported as the means with standard deviation (SD ± X). Statistical analysis for regression also performed to evaluate the best fit kinetic model for release pattern of formulated tablets. Furthermore, the variance in released pattern among different formulations was evaluated by applying one-way analysis of variance (Anova test) at 0.05 level of significance using SPSS (version 23).

RESULT AND DISCUSSION

Formulations development and optimization has been performed with the exploration of new excipients to prepare modified drug release system from simple dosage forms. The direct compression method is the most widely used method for formulation of controlled-release tablets. This technique is more effective especially when the formulation contains the low ratio of active ingredients with hydrophobic nature.

Micromeritics Properties of Powder Blends

The values of angle of repose were found within the range of 26.2 ± 0.12 to 40.4 ± 0.03 which reflects the excellent flowability of powder blend. The results of Carr's index and Hausner ratio were ranged from 16.4 to 22.5% and 1.14 to 1.27 respectively as presented in Table **2**. These all micromeritics properties of powder blend indicated good flow characters of the blends and were suitable for formulation of sustained release furosemide tablets using direct compression method.

Physical Evaluation of Tablets

The results of all physical tests including thickness, diameter, hardness, weight variation, friability are presented in Table **3**. The relative standard deviation (SD) of weight was below 5% and SDs was uniform and found within the range of 0.54 to 1.55 for all formulated tablets. The obtained data of thickness and diameter test indicates that minimal variation among all controlled release tablets ranged from 3.24 ± 0.17 to 3.87 ± 0.07 mm and 6.05 ± 0.21 to 6.97 ± 0.52 mm thicknesses and diameters respectively. It was also observed that slight increase in thickness with increasing concentration of HPMC which reflect low binding affinity of all grades of HPMC used in different formulations. The formulations prepared by different sustained release materials had friability within range of 0.03 ± 0.09 to 0.49 ± 0.11%. Formulations contained waxy materials showed very low friability (≤0.3) while tablets containing HPMC exhibited higher friability with an increase in HPMC concentration as indicated in Table **3**. The hardness of formulated furosemide tablets was found within the range of 4.21 ± 0.35 to 6.64 ± 0.03 kg. The hardness of formulated tablets containing HPMC was found to be high than the hardness of tablets prepared using waxy materials. In case of HPMC as the proportion of HPMC increased in the formulation its hardness also increased.

Table 2. Micromeritics properties of different formulations of furosemide.

Batch code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Hausner's ratio	Angle of repose (^{0})	Results (USP, 2007)
F1	0.51 ± 0.06	0.64 ± 0.03	20.1 ± 0.08	1.23 ± 0.10	30.3 ± 0.09	Excellent
F2	0.50 ± 0.02	0.62 ± 0.04	18.3 ± 0.04	1.20 ± 0.12	29.6 ± 0.17	Excellent
F3	0.52 ± 0.06	0.64 ± 0.07	21.5 ± 0.03	1.23 ± 0.07	31.4 ± 0.08	Good
F4	0.48 ± 0.04	0.57 ± 0.03	17.4 ± 0.07	1.15 ± 0.04	26.2 ± 0.12	Excellent
F5	0.51 ± 0.05	0.63 ± 0.06	20.4 ± 0.12	1.23 ± 0.07	33.4 ± 0.07	Good
F6	0.54 ± 0.09	0.65 ± 0.06	21.4 ± 0.06	1.26 ± 0.13	40.1 ± 0.12	Fair
F7	0.50 ± 0.07	0.62 ± 0.03	19.8 ± 0.06	1.24 ± 0.14	36.2 ± 0.13	Fair
F8	0.51 ± 0.10	0.62 ± 0.06	19.5 ± 0.06	1.23 ± 0.15	37.7 ± 0.12	Fair
F9	0.52 ± 0.08	0.64 ± 0.04	22.5 ± 0.09	1.27 ± 0.10	31.8 ± 0.03	Good
F10	0.47 ± 0.11	0.56 ± 0.05	16.4 ± 0.13	1.15 ± 0.13	29.5 ± 0.11	Excellent
F11	0.51 ± 0.08	0.64 ± 0.03	21.4 ± 0.14	1.23 ± 0.06	34.0 ± 0.05	Good
F12	0.50 ± 0.09	0.62 ± 0.02	21.3 ± 0.07	1.26 ± 0.07	40.4 ± 0.03	Fair
F13	0.51 ± 0.08	0.63 ± 0.09	20.5 ± 0.05	1.24 ± 0.12	33.8 ± 0.12	Good
F14	0.49 ± 0.05	0.60 ± 0.06	19.7 ± 0.11	1.24 ± 0.07	31.2 ± 0.10	Good
F15	0.50 ± 0.08	0.62 ± 0.07	19.1 ± 0.07	1.20 ± 0.14	35.5 ± 0.07	Good
F16	0.49 ± 0.07	0.60 ± 0.04	20.3 ± 0.05	1.23 ± 0.12	30.8 ± 0.04	Excellent
F17	0.50 ± 0.09	0.60 ± 0.06	18.4 ± 0.12	1.14 ± 0.06	28.2 ± 0.06	Excellent
F18	0.51 ± 0.07	0.63 ± 0.04	20.3 ± 0.07	1.23 ± 0.10	30.5 ± 0.08	Excellent

Table 3. Physicochemical evaluation of different furosemide sustained release formulations.

S. No	Batch code	Testing Parameters					
		Thickness (mm)	Diameter (mm)	Hardness (Kg)	Weight variation (mg)	Friability (%)	Assay (%)
1	F1	3.38 ± 0.09	6.21 ± 0.71	4.83 ± 0.41	305.8 ± 1.10	0.29 ± 0.04	102.5 ± 2.6
2	F2	3.61 ± 0.05	6.38 ± 0.83	4.64 ± 0.53	406.3 ± 0.85	0.17 ± 0.02	95.9 ± 2.8
3	F3	3.85 ± 0.03	6.44 ± 0.54	4.33 ± 0.32	505.8 ± 0.98	0.10 ± 0.08	103.1 ± 2.8
4	F4	3.32 ± 0.01	6.05 ± 0.21	4.21 ± 0.35	305.5 ± 0.89	0.25 ± 0.25	100.1 ± 1.5
5	F5	3.51 ± 0.07	6.24 ± 0.56	4.23 ± 0.89	405.8 ± 0.54	0.03 ± 0.09	101.1 ± 3.8
6	F6	3.79 ± 0.06	6.30 ± 0.35	4.38 ± 0.25	505.7 ± 0.96	0.04 ± 0.07	97.5 ± 1.8
7	F7	3.45 ± 0.10	6.97 ± 0.52	4.96 ± 0.78	305.5 ± 0.87	0.19 ± 0.04	98.4 ± 2.5
8	F8	3.67 ± 0.05	6.15 ± 0.63	4.57 ± 0.75	405.9 ± 0.98	0.16 ± 0.07	95.9 ± 4.2
9	F9	3.87 ± 0.07	6.43 ± 0.35	4.79 ± 0.26	506.1 ± 1.55	0.08 ± 0.08	101.0 ± 4.1
10	F10	3.24 ± 0.17	6.92 ± 0.35	6.12 ± 0.04	306.5 ± 0.89	0.32 ± 0.05	99.5 ± 3.6
11	F11	3.51 ± 0.05	6.11 ± 0.35	6.31 ± 0.05	405.4 ± 0.97	0.41 ± 0.05	98.9 ± 2.5
12	F12	3.62 ± 0.03	6.27 ± 0.24	6.64 ± 0.03	506.2 ± 0.87	0.49 ± 0.11	102.0 ± 2.8
13	F13	3.34 ± 0.04	6.28 ± 0.54	6.01 ± 0.46	305.9 ± 1.02	0.30 ± 0.08	101.1 ± 1.5
14	F14	3.42 ± 0.03	6.10 ± 0.46	6.20 ± 0.11	406.1 ± 0.96	0.45 ± 0.10	102.1 ± 3.8
15	F15	3.50 ± 0.02	6.14 ± 0.64	6.50 ± 0.11	506.3 ± 0.89	0.46 ± 0.13	99.5 ± 1.8
16	F16	3.32 ± 0.04	6.35 ± 0.25	6.11 ± 0.11	305.8 ± 0.92	0.27 ± 0.05	96.4 ± 2.5
17	F17	3.43 ± 0.05	6.11 ± 0.46	6.25 ± 0.12	405.4 ± 1.03	0.36 ± 0.08	94.9 ± 4.2
18	F18	3.51 ± 0.05	6.38 ± 0.75	6.44 ± 0.01	506.3 ± 0.94	0.47 ± 0.12	98.5 ± 3.2

The drug content results of formulated controlled released tablets are illustrated in Table **3**. The achieved results showed that the content of furosemide in different controlled released formulations prepared by direct compression method was in the range of 94.9 ± 4.2 to 103.1 ± 2.8 %. The obtained results indicated that all formulated tablets were within USP ranges for drug content.

In 0.1 N HCl at pH 1.2, all formulations showed very less amount of drug release due to the very low solubility of furosemide reported at pH 1.2 approximately less than 4×10^{-4} % w/v at pH 1.2 [14]. However, most of the formulations displayed complete but sustained drug release in phosphate buffer medium (pH 6.8) which means that drug dissolution depends on solubility of drug at different pH ranges. The pH-dependent solubility of furosemide was also reported. The release of furosemide from sustained release formulations varied with respect to the types and proportion of

matrix forming materials. The hydrophilic xanthan gum containing formulations showed an excellent released pattern of furosemide up to 12 hrs. There is no significant difference observed in the released pattern with respect to the concentration of natural gum (as shown in Figure **1**).

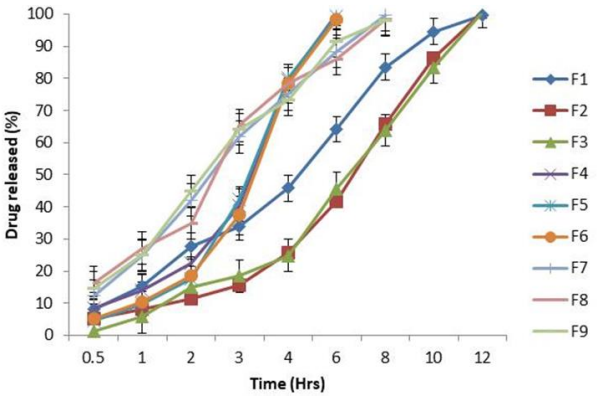

Figure 1. Percentage drug released of sustained release formulations containing natural polymers.

This retarding capability of gum take place may be due to the opposing nature of drug and gum i.e. hydrophobic and hydrophilic nature of drug and gum respectively. In contrast, hydrophilic bees wax consists of 70-75% of a mixture of various esters from C26-C32 alcohols, particularly d-β-dehydropalmitic, palmitic, hydroxypalmitic, and cerotic acid, which could not impart any sustaining effect on furosemide release. Bees wax when used as matrix former, 80% of furosemide in the matrix system was virtually released within the 4 hours of dissolution. In all the three ratios, bees wax was only able to prolong the drug released from the formulated tablets only up to 6 hrs. A similar type of results was reported in a previous study [15]. The hydrophilic carnauba wax composed of alkyl esters of wax acids (80%), chiefly myricyl cerotate, free monohydric alcohols (10%), lactose and resin. This matrix system released around 88% drug after 6-hour of dissolution period. However, an extensive burst release was observed with this system. The esters of these wax acids help in the formation of different surface bonds i.e. hydrogen bonds between a water molecule and the wax ingredients due to the presence of more electronegative oxygen in the ester moiety. This facilitated the formation of surface bonds can be attributed to lower sustaining effect imparted by these wax which was also reported by Quadir *et al*. in a previous study [15]. Furthermore, it was observed that 60-80% of the drug was released after 8 h from F10 formulation (Drug: HPMC-K4M, 1:1) than slightly decreased and a sustained release pattern was observed up to 12 hrs. It is also found that formulation contained 1:1 ratio of drug-polymer showed much higher drug release rates in the range of 99.9 to 84.0% as compared to 1:2 and 1:3 ratios i.e. 93.4 to 76.8% and 84.0 to 72.0% respectively. The drug release from the HPMC grades were found to decrease in the following order K4M > K15M > K100M (as shown in Figure **2**).

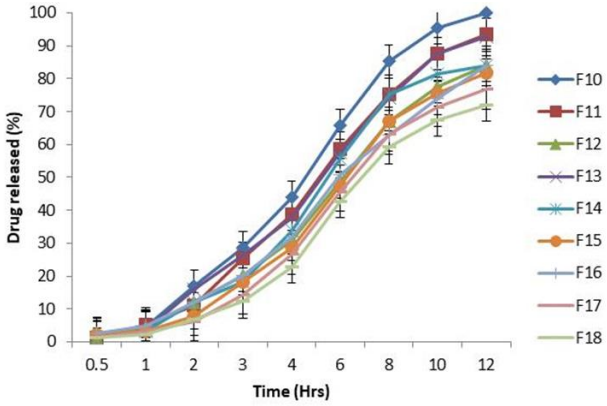

Figure 2. Percentage drug released of sustained release formulations containing synthetic polymers.

All three grades of HPMC used in formulations, the patterns of drug released were (99.98 ± 0.57 to 84.08 ± 1.57) for low viscosity grade K4M, (92.98 ± 0.27 to 81.98 ± 0.07) for K15M and (84.08 ± 0.77 to 72.01 ± 0.97) observed in K100M grade HPMC. Similarly, Ulla et al. reported these types of results in the study of formulation SR tablets of lornoxicam [16].

Kinetics Models Studies

According to mathematical kinetics models, the regression value (r^2) indicates the release pattern and mechanism of drug according to the best-fit kinetic model. The release pattern and mechanism of the drug of all six best formulations was best-fit for zero-order kinetics while most of the formulations were follow Korsmeyer-Peppas and Higuchi models for the mechanism of drug release (as shown in Table **4**). However, these all mathematical models for drug release are all empirical and there is no conclusive evidence found about release pattern and mechanism of drugs.

Table 4. Drug release kinetics models of furosemide sustained release formulation.

S. No	Batch Code	Drug Release Kinetic Models (R^{2*})			
		Zero order	Higuchi	Korsmeyer-Peppas	Hixson-Crowell
1	F1	0.9754	0.9884	0.9940	0.9658
2	F2	0.9883	0.9410	0.9680	0.7766
3	F3	0.9945	0.9548	0.9944	0.9925
4	F10	0.9574	0.9877	0.9588	0.9788
5	F11	0.9689	0.9880	0.9749	0.9963
6	F13	0.9738	0.9940	0.9556	0.9962

Table 5. Statistical analysis results of One-way Anova results for release profile of all formulations.

Variation Source	Sum of Squares	Df*	Mean Square	P-value	F-value
Between Groups	9010.457	17	530.027		
Within Groups	25.905	90	0.518	0.000	6.272×10^{31}
Total	9036.362	107			

Degree of freedom
P<0.05

The results of the statistical analysis were given in Table **5**. The results of one-way ANOVA test indicate that there is a significant difference observed in release pattern of sustained release formulations ($p<0.05$).

CONCLUSION

Dissolution studies results indicated that the furosemide release from formulated tablets was not generally similar and constant for all formulations containing different control releasing materials. Overall decrease in furosemide release rate with respect to decrease in ratio of HPMC in formulations. The initial burst of matrix tablets had been seized using high viscosity grades polymers. Among all the developed formulations, the xanthan gum and different grades of HPMC containing formulations showed non-fickian drug release pattern. Furthermore, these two polymers showed constant and controlled release rate and no alteration were observed up to 12 hrs. Direct compression utilizes the smallest amount of machinery and man power.

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