INTRODUCTION

The oral route of drug administration is the most acceptable and frequently used route because of the convenience of self-administration, ease of manufacturing and a high degree of dose accuracy.[1] Oral dosage forms are designed by exploiting the unique features of gastro-intestinal tract as the drug have to pass from the walls of GIT before getting access into systemic circulation.[2] Pharmaceutical industry is focusing on the establishment of novel drug delivery systems rather than to investigate and develop new drug entities due to increased Investigational cost of a new drug.[3] Over the past several decades controlled release technology has rapidly emerged as a drug delivery system that offers novel approaches for the delivery of bioactive compounds into systemic circulation at a predetermined rate that significantly improves drug bioavailability and clinical outcomes with decreased toxicity. Sustained release dosage forms are designed in such a way that the rate of drug release from the tablet matrix occurs in a controlled manner over an extended period of time maintaining a constant plasma drug level thus improving patient compliance and effective clinical outcomes.[4] A constant therapeutic drug level is maintained throughout the dosing intervals which often prolongs the onset of pharmacological action.[5]

The development of sustained drug delivery system is a challenging task in terms of not only to provide a constant drug release profile but also to retain the dosage form in the stomach or upper small intestine until all the drug is completely released in the desired time.[6] An ideal oral drug delivery system will steadily release a measurable and reproducible amount of the drug over an extended period of time.[7] Several mechanisms are involved in the release of drugs from controlled release formulations such as, dissolution controlled release system and diffusion controlled release systems. In dissolution controlled systems, dissolution is the rate controlling step. The drug is embedded in slowly dissolving or erodible matrix or by coating it with slowly dissolving substances, while in diffusion controlled release systems the release rate of drug is dependent on its diffusion through inert water insoluble membrane barrier. In matrix diffusion controlled devices, the therapeutic agent is dispersed in an insoluble matrix of rigid non-swellable hydrophobic materials or a swellable (soluble) hydrophilic substance. Among different strategies to prolong the drug action, formulation of matrix tablet has gained immense popularity because it

has the advantage of simple processing and a low cost of fabrication.[8] Matrix tablets are cost effective, easy to prepare and exhibit predictable release behavior.

Polymers are becoming increasingly important in the field of drug delivery. They owe their unique properties to their size, three-dimensional shape and asymmetry. Polymers occur naturally (biopolymers) as well as synthesized in the Laboratory on large scale. Advances in polymer science have led to the development of several novel drug-delivery systems.[9] The chemical reactivity of polymers depends to a large extent on the way the monomer units are put together. Polymers can be used in film coatings to mask the unpleasant taste of a drug, to enhance drug stability and to modify drug release characteristics. Discovery of polymers with ideal properties still provides new avenues in pharmaceutical research.

Studies have shown that the rate and extent of drug release depends on the type and level of the excipient/polymer used. Many polymers have been used in the formulation of matrix based sustained release drug delivery systems. The water-soluble polymers are widely being used in the designing of matrix systems in order to provide a sustained drug delivery because of their excellent drug retarding ability, low cost, and broad regulatory acceptance.[10,11] Hydrophilic polymers are usually not affected by variation in pH therefore releasing the drug at a constant rate from oral dosage forms. However, in case of water soluble drugs, the use of hydrophilic polymers alone for prolonging drug release is restricted because of the leakage of dissolved drug from the hydrophilic gel network through diffusion, hence a blend of hydrophilic and hydrophobic polymers is recommended for such drugs.[12] Among cellulose ether derivatives Hydroxypropyl methylcellulose has been widely investigated for its drug releasing effect as compared to methylcellulose and Hydroxypropyl cellulose.[13]

CMC described by the USP as sodium salt of poly carboxymethyl ether of cellulose. CMC or cellulose gum often used as a sodium salt is a derivative of cellulose (a beta-glucopyranose polymer) with carboxymethyl groups (-CH_2-COOH) attached to the hydroxyl groups of the glucopyranose backbone. It occurs as white, odorless, granular powder having molecular formula [C_6 H_7 O_2 (OH) $_2$ CH_2 COONa] n. Fig. 1 indicates the chemical structure of CMC sodium. A number of grades of CMC sodium are available such as Accelerate. Grades are typically classified as being of low, medium or high viscosity.

Hydroxypropyl methyl cellulose (HPMC) (also known as hypromellose) is propylene glycol ether of Methylcellulose. It is a semi synthetic, inert, visco-elastic polymer used as an ophthalmic lubricant, as well as an excipient and controlled-delivery component in oral medicaments. HPMC is the most important hydrophilic carrier material used in the preparation of oral controlled drug delivery systems because of its non-toxic nature, ease of compression and accommodation to high level of drug loading.[14] Fig. 2 represents the chemical structure of HPMC.

Hydroxypropyl cellulose (HPC) is a derivative of cellulose soluble in both water and organic solvents. It has the property to retain water by forming a film that prevents water loss and exhibit greater drug retarding properties than Hydroxyethyl cellulose. The drug release from HPC matrices is controlled primarily by diffusion through pores and channels in the structure.[15] Hydroxypropyl cellulose is generally used as an emulsifier, thickening agent and film former in tablet coatings because of its surface properties but it lacks the property to form gel because it forms open helical coils. Fig. 3 indicates the chemical structure of HPC.

Medicinal products of the prokinetics class are found to be effective in the treatment of all clinical forms of dyspepsia.[16] Levosulpiride being a gastroprokinetic agent has shown promising results in the treatment of various gastric disorders like functional dyspepsia and non-erosive reflux disorder.[17] Chemically it is a synthetic benzamide derivative having strong inhibitory effect on the dopaminergic D_2 receptors both in the central nervous system (CNS) and in the gastrointestinal tract.[18] Studies have shown Levosulpiride to be effective in the treatment of various diseases like dyspepsia (functional or organic), diabetic gastroparesis, reflux esophagitis, iatrogenic emesis induced by drugs like chemotherapy, calcitonin and anesthetics as well as non-iatrogenic nausea and vomiting.[19] It also acts as a moderate agonist at the serotonergic 5-HT_4 receptor and to a lesser extent on 5-HT_3 receptor.[20,21] The serotonergic (5-HT_4) component of Levosulpiride may enhance its therapeutic efficacy in gastrointestinal disorders.[22] This property, together with antagonism at D2 receptors, may contribute to its gastrointestinal prokinetic effect.[17] In a randomized, double-masked trial, it was found that Levosulpiride has similar effect to cisapride in the treatment of dysmotility-like functional dyspepsia.[23] The drug is given mostly in the dose of 25-50mg three times a day because of its short half-life which leads to poor patient compliance and adverse drug effects. Fig. 4 represents the structure of Levosulpiride.

The aim of the current work was an attempt to develop sustained release matrix tablets of Levosulpiride for improved patient compliance and better therapeutic effects of various polymers with different polymeric compositions. Various physical tests were performed for the formulated tablets such as weight variation, thickness, hardness test and friability test. The tablets were evaluated for uniformity of active ingredients by performing a pharmaceutical assay. The release of the model drug from the developed matrix tablets was performed in USP phosphate buffer of pH (6.8). The mechanism of drug release was studied by subjecting drug release data to various kinetic models.

MATERIALS AND METHODS

Chemicals

For the preparation of matrix tablets of various polymeric compositions, Methocel E-5 (Hydroxypropyl methyl cellulose), HPC (Hydroxypropyl Cellulose) and Sodium Carboxymethyl cellulose sodium (CMC) were used as polymers respectively. MCC PH-200 (Microcrystalline Cellulose) was used as bulking agent for tablets. Talcum and Magnesium Stearate were used as lubricants respectively. De-ionized Water and 0.1N NaOH solution were used as solvents. Potassium dihydrogen phosphate, sodium chloride and all other chemicals used were of analytical grade.

Preparation of the Matrix tablets

Levosulpiride tablets were formulated and evaluated at Aims Pharmaceuticals (pvt) Ltd. Kahuta triangle industrial area Islamabad Pakistan, where all the tablet manufacturing equipment and testing instruments were available. Table 1 indicates the composition of all matrix formulations of the model drug (Levosulpiride). To formulate tablets, the model drug, polymers and excipients (except glidants and lubricants) were first passed individually from mesh # 16 and then mixed for 15min. The contents were mixed for further 5min after the addition of lubricants and glidants. The bulk was then compressed into tablets using a ZP-17 tablet compression machine (Shanghai Tianfeng China). Before subjecting the bulk to the various physical tests, the micrometric properties of the powders was determined. The prepared formulations of the model drug were then evaluated for the various physical parameters.

CHARACTERIZATION

Micrometric properties of powders

The powder flow plays an important role in manufacturing of a fine tablet. The flow properties of the powder blends were evaluated by determining the bulk density, tapped density and angle of repose.

Bulk density

To measure the bulk density, pre-sieved powder blend was carefully poured into a dry graduated cylinder without compaction and the weight and volume was measured. The unit of bulk density is g/mL and is given by

$$D_b = \frac{M}{V_0}$$

Where, M represents the mass of powder and V_0 represents the Bulk volume of the powder.

Tapped density

Tapped density was calculated by pouring a known mass of powder blend in a graduated cylinder placed on a mechanical tapping apparatus. The compact volume of the powder after tapping was measured. Tapped density is also expressed as g/mL and is given by

$$D_t = \frac{M}{V_t}$$

Where, M represents the mass of powder and V_t is the tapped volume of the powder.

Angle of repose

Funnel method was adopted to measure the angle of repose. The powder was allowed to drop from the funnel to form a cone to a maximum height. The diameter of the heap (D) and height of the heap (h) was measured and the angle of repose (Ɵ) was calculated using formula

$$Tan\theta = \frac{h}{r}$$

$$\theta = Tan^{-1}(\frac{h}{r})$$

Where, h is the height in cm, r is the radius and Ɵ is the angle of repose.

Weight variation

The weight variation of tablets was calculated as per method described in the B.P by using electronic balance (Sartorius). The individual weights were then compared with average weight for determination of weight variation.

Hardness or crushing strength of tablets

The hardness test represents the structural integrity and the point at which the tablet breaks during storage, transportation and handling before usage. Moreover, hardness of the tablet also effects the disintegration time. The hardness was measured using Digital Hardness tester.

Thickness of tablets

Variation in tablet thickness may cause problems during counting and packaging. The thickness of tablets was determined by using Vernier caliper.

Friability of tablets

Tablets from each formulation were selected randomly and weighed. The pre-weighed tablets were then placed in the plastic chamber of Roche friabilator. The friabilator allows the tablets to face a combined effect of abrasion and shock in the plastic chamber revolving at 25 rpm. After four min (100 revolutions) tablets were removed, de-dusted and weighed again. The following formula was used to calculate the friability of the tablets.

$$\frac{W_1 - W_2}{W_1} \times 100$$

Where W_1 is the initial weight of the tablets and W_2 is the final weight.

Content uniformity of tablets

The tablets were also evaluated for the content uniformity by randomly selecting specific number of tablets from each formulation and weighed on a suitable tare container. The tablets were then powdered using pestle and mortar and solution of Levosulpiride was prepared in a 100mL volumetric flask by dissolving the powder equivalent to 25mg of Levosulpiride in 0.1N NaOH. Further dilutions were made and

the absorbance of resultant solutions was measured against the standard at a wavelength of 214nm by using UV/Visible spectrophotometer.

Calculations

$$\%Assay = \frac{A_1}{A_2} \times 100$$

Where

A_1 = Absorbance of sample

A_2 = Absorbance of working standard

***In-vitro* drug release studies**

Dissolution test was performed using dissolution test apparatus USP type II (Pharma test Germany) in Phosphate buffer solution (PH 6.8) for all nine formulations of Levosulpiride. For this purpose, 900mL of buffer solution was placed in each vessel of the dissolution test apparatus and the solution was allowed to reach a temperature of 37°C. Single tablet of Levosulpiride was placed in each vessel of the dissolution test apparatus and the apparatus was operated at a rate of 50rpm. 5mL of the sample was collected from each vessel after defined intervals and was filtered and diluted with the dissolution medium. After each sampling fresh dissolution medium was added to the vessels in order to maintain the volume of the dissolution medium.[24] Absorbance of the samples and standard were then measured with the help of UV-visible spectrophotometer.

FTIR Spectroscopy

The structure and intermolecular interactions between components of the tablet were investigated by Fourier transform infrared (FTIR) spectroscopy. FTIR spectra of tablet and individual components were recorded with a Thermo-Fischer Scientific Nicolet 6700 FTIR spectrometer at 8cm^{-1} resolution averaging 256 scans. The spectra were collected over the 4000–400 cm^{-1} range.

Drug Release Kinetics

To evaluate the kinetics and *in-vitro* drug release data different mathematical models were used including Zero order rate equation which describes the system where the drug release rate is independent of its concentration.[25]

$$Q = k\,t \qquad (1)$$

Where Q is amount of un-dissolved drug at time t, K is zero order rate constant and t is time.

The First order rate equation describes the system where drug release rate is dependent on its concentration.[26]

$$LogC = LogC_0 - kt / 2.303 \qquad (2)$$

Where, C_0 is the initial concentration of drug and K is first order constant.

Higuchi model is an invaluable framework and used for developing a number of drug delivery systems. A direct relationship between amount of drug released from matrix system and square root of time is established using the Higuchi model.[27] It is expressed in equational form as under

$$Q = K\sqrt{t} \qquad (3)$$

Where "Q" represents the percent of drug released in "t" time, "K" is Higuchi's constant and "t" is the time.

The Hixson-Crowell cube root law describes the drug release from systems where there is a change in surface area and diameter of particles or tablets.[28] Mathematical expression of this model is as under

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC}\,t \qquad (4)$$

Where, "Q_0" is the initial amount of the drug in tablet, "Q_t" is the amount of drug released in time "t", and K_{HC} is the Hixson-Crowell rate constant.

A simple relationship to describe the release behavior of a drug from hydrophilic matrix system was developed by Korsmeyer Peppas which is mathematically expressed as,

$$M_t / M_\alpha = K_{kp} t^n \qquad (5)$$

Where Mt / Mα is the fraction of drug released at time t, K_{kp} is the rate constant incorporating the properties of macromolecular polymeric system and drug while n is the release exponent used to characterize the transport mechanism.[29] The n value is used to describe various release mechanisms for cylindrical shape devices as shown in Table 2.

RESULTS AND DISCUSSION

Flow Properties of Powders

The particle size of powders was found to be in the range of 760-890µm which resulted in free flow properties of powders. The data given in Table 3 shows that the angle of repose for all formulation is <30 which clearly depicts that granules have excellent flow characteristics.

Weight Variation

The standard weight of Levosulpiride tablet was selected to be 200mg and standard limit for weight variation was set to be ± 5%. Twenty tablets from each formulation were selected and individual tablet weight was calculated. The results shown in Table 4 indicates that all the results are lying within the specified range which is also studied previously by Abdel-Rahman *et al*[30].

Hardness of Tablets

It is better considered that the hardness of uncoated tablets should not be less than 5kg/cm^2. A minimum of 6 tablets should be tested for hardness. Ten tablets from each formulation were selected and their hardness was calculated. According to Table 4 the average hardness of the tablets of all formulations is within the specified range as previously described by Vueba *et al*[13].

Thickness of tablets

Ten tablets from each formulation were taken and average thickness values were calculated. The usual range of tablets thickness weighing up to 250mg is 3mm - 4mm. According to the results indicated in Table 4, the average thicknesses of the tablets of all formulations are within the specified limits.

Friability of Tablets

The friability of tablets should be less than 1%. Twenty tablets from each formulation were selected at random and their percent friability was calculated. According to the results shown in Table 4 all results are laying within the specified limits.

Content uniformity of tablets

Twenty tablets from each formulation were selected randomly. Table 4 represents the content uniformity of each formulation and it is evident from the Table that each formulation lies within the official limits i.e 95-105%.

***In-vitro* drug release studies**

To study the *in-vitro* drug release behavior from polymer matrix in simulated intestinal medium, dissolution studies were carried out for all formulations. The dissolution test was carried out using USP type II dissolution apparatus. The tablets were placed in 900mL of phosphate buffer solution maintained at 37±1°C and the apparatus was operated at 50 rpm for 8hrs. To study the effect of polymer on drug release the polymer drug ratio was altered. The formulations F1, F2 & F3 contain HPMC, F4, F5 & F6 contain HPC while F7, F8 and F9 contain CMC sodium in an increasing order of polymer drug ratio. The percentage of drug release from the matrix tablets as shown in Table 5 indicates that the drug release from the formulations reduces as the polymer ratio is increased irrespective of the type of polymer used. The data also shows that Levosulpiride release from the matrix tablet was sustained over an extended period of time at pH 6.8 and the sequence of retarding the drug release was found to be CMC sodium > HPC > HPMC. CMC sodium among the three polymers proved to be the best retarding material and formulation 9 was found to be the best one. Fig. 5-7 indicates the individual *in-vitro* drug release profile of all the developed matrix tablet samples. Fig. 8 represents the cumulative % release of all the formulations.

FTIR Spectroscopy

FTIR spectra of pure Levosulpiride, CMC sodium and their blend are given in Fig. 9, 10 and 11 respectively. The FTIR spectrum of Levosulpiride demonstrates sharp transmittance bands for (C-H) at 2810cm^{-1} which also appears in the final spectrum. The characteristic (–OH/–NH) bands in Levosulpiride at 3124cm^{-1} and 3367cm^{-1} also shifted to short and broader peaks which depicts about the involvement of these groups in interfacial H-bonding between the components. The other important contributions from Levosulpiride are the presence of amide I band corresponding to (C=O) vibration of acetyl group at ∼1623cm^{-1} and (C–N) stretching vibration at ∼1060cm^{-1} which can be seen in CMC sodium as well. The FTIR spectroscopy reveals that no chemical interaction occurred between the components.

Drug Release Kinetics

Using various kinetic models like Zero order, First order, Higuchi Model, Hixon-Crowell Model and Korsmeyer–Peppas Models, drug-release kinetics was

investigated. The values of drug-release constant (k) and regression coefficient (r) were obtained from Zero order, First order, Higuchi, Hixon-Crowell Model and Korsmeyer–Peppas models.

To examine the drug release mechanism, the data obtained from all nine formulations was fitted into various kinetic models like, zero order, first order, Higuchi's, Hixon-Crowell and Korsmeyer-Peppas exponential equation. The results obtained from these kinetic models are presented cumulatively in Table 6. It is evident from the data that the formulations released the drug according to Higuchi's pattern. The "n" value for all formulations was found to be greater than 0.5 which according to Peppas model approximates non-Fickian diffusion mechanism as shown in Table 6.

Fig. 12-14 indicates the graph for Higuchi Model for formulations 07-09.

CONCLUSION

Sustained release tablets of Levosulpiride were prepared successfully using polymers like HPMC, HPC and CMC sodium in varying concentrations. The particle size and drift behavior of the granules were found to be in accordance with the official standards. Direct compression method was selected on the basis of Good compressibility index of the granules. The physical properties of compressed tablets like thickness, hardness, weight variation and friability were in compliance to the official limits. The free flowing powder facilitates the formation of tables with ideal properties. The drug release was primarily controlled by the type and concentration of polymers and a slight change in polymer concentration resulted in altered drug release. On the basis of these results it can be concluded that the drug release can be further prolonged if the polymers are used in combination because of their possible interaction and subsequent cross-linking. The kinetic model which best fits to the release data was found to be Higuchi's equation followed by zero order with non-fickian behavior over 8hrs period. The objective of the study was met through the formulation of a novel sustained release formulation of Levosulpiride which will help in reducing dosing frequency, plasma drug level fluctuation, dose related adverse effects and improving patient compliance. These prepared tablets can be evaluated in future for their stability studies and *in-vivo* behavior moreover to develop an *in-vitro in-vivo* correlation (IVIVC).

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Conflict of interests

Declared None

Tables:

Table 1. Formulation Sheet of Levosulpiride sustained release (SR) tablets.

Formulation	Drug (Levosulpiride) (%)	Polymers		MCC (%)	Talc (%)	Mg Stearate (%)
		Name	(%)			
F1	12.5	HPMC (K100LV)	50	35	1.25	1.25
F2	12.5	HPMC (K100LV)	65	20	1.25	1.25
F3	12.5	HPMC (K100LV)	75	10	1.25	1.25
F4	12.5	HPC (K100M)	50	35	1.25	1.25
F5	12.5	HPC (K100M)	65	20	1.25	1.25
F6	12.5	HPC (K100M)	75	10	1.25	1.25
F7	12.5	CMC Sodium	50	35	1.25	1.25
F8	12.5	CMC Sodium	65	20	1.25	1.25
F9	12.5	CMC Sodium	75	10	1.25	1.25

MCC, Microcrystalline cellulose. HPMC, Hydroxypropyl methyl cellulose. HPC, Hydroxypropyl Cellulose. CMC, Carboxymethyl cellulose, Mg Stearate, Magnesium Stearate

Table 2. Diffusion exponent and solute release mechanism for various systems

Diffusion Exponent	Solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

Table 3. Evaluation of Powder flow for Levosulpiride Sustained release tablets.

S. No	Formulation	Angle of Repose	Bulk density (g/ml)	Tapped density (g/ml)
1	**F1**	29.01 ± 0.18	0.700 ± 0.02	0.830 ± 0.001
2	**F2**	28.76 ± 0.09	0.730 ± 0.05	0.850 ± 0.003
3	**F3**	28.13 ± 0.18	0.718 ± 0.01	0.865 ± 0.002
4	**F4**	29.22 ± 0.18	0.747 ± 0.04	0.889 ± 0.006
5	**F5**	25.01 ± 0.18	0.710 ± 0.02	0.836 ± 0.001
6	**F6**	24.76 ± 0.09	0.735 ± 0.05	0.854 ± 0.003
7	**F7**	29.13 ± 0.18	0.713 ± 0.01	0.869 ± 0.002
8	**F8**	28.22 ± 0.18	0.765 ± 0.04	0.881 ± 0.006
9	**F9**	27.01 ± 0.18	0.701 ± 0.02	0.840 ± 0.001

All data are reported as mean± standard deviation, n= 3 per experiment

Table 4. Evaluation of Levosulpiride sustained release (SR) tablets.

Formulation	Average weight (mg)	Average hardness (kg)	Average thickness (mm)	Friability (%)	Assay (%)
F1	205	6.5	3.40	0.52	97
F2	201	6.4	3.56	0.74	101
F3	200	6.3	3.60	0.46	102
F4	198.9	6.2	3.90	0.28	95
F5	202	7.0	3.80	0.19	98
F6	199.6	6.9	3.80	0.48	102
F7	199	6.8	3.62	0.67	97
F8	202	7.0	3.62	0.43	103
F9	200	6.9	3.62	0.22	98

All data are reported as mean± standard deviation, n= 3 per experiment

Table 5. *In-vitro* Drug Release data from compressed Matrix tablets of Levosulpiride.

S. No	Formulation	Percentage release of Levosulpiride			
		1st Hour	2nd Hour	4th Hour	8th Hour
1	**F1**	43.22%	53.52%	65.96%	76.44%
2	**F2**	41.02%	50.27%	59.39%	66.68%
3	**F3**	24.64%	34.18%	44.14%	54.40%
4	**F4**	42.28%	57.61%	62.98%	72.55%
5	**F5**	38.26%	44.81%	51.91%	60.41%
6	**F6**	24.53%	29.79%	37.90%	45.82%
7	**F7**	37.48%	47.81%	59.90%	69.42%
8	**F8**	26.95%	36.93%	46.56%	56.95%
9	**F9**	13.18%	21.99%	29.71%	39.66%

All data are reported as mean± standard deviation, n= 3 per experiment

Table 6. Data showing *in-vitro* release kinetics of various formulations of Levosulpiride in buffer pH 6.8.

Formulation	Zero order		First order		Higuchi		Hixon-Crowel		Korsmeyer Peppas		Result
	R^2	K	R^2	K	R^2	K	R^2	K	R^2	n	
F1	0.680	7.705	0.865	-0.160	0.976	18.04	0.887	0.097	0.993	0.864	AM
F2	0.620	6.512	0.764	-0.116	0.989	13.74	0.859	0.078	0.994	0.881	AM
F3	0.782	5.817	0.875	-0.088	0.981	16.01	0.884	0.115	0.991	0.871	AM
F4	0.664	7.237	0.834	-0.140	0.976	16.43	0.889	0.091	0.994	0.881	AM
F5	0.620	5.815	0.748	-0.095	0.991	11.94	0.927	0.074	0.990	0.876	AM
F6	0.729	4.703	0.748	-0.095	0.992	11.72	0.927	0.091	0.993	0.864	AM
F7	0.699	7.105	0.849	-0.131	0.969	17.31	0.872	0.100	0.990	0.881	AM
F8	0.761	6.005	0.864	-0.093	0.979	16.03	0.882	0.110	0.991	0.871	AM
F9	0.870	4.491	0.918	-0.058	0.998	14.09	0.872	0.134	0.993	0.881	AM

AM = Anomalous

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