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FORMULATION AND *IN VITRO* EVALUATION OF APREMILAST SUSTAINED RELEASE MATRIX TABLETS

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Abstract:

The purpose of the present study was to formulate and evaluate of sustained release tablets of Apremilast. Sustained release tablets of Apremilast were formulated with different concentrations of HPMC K 15,Sodium CMC and Guar Gum by using direct compression method and evaluated for the different evaluation parameters such as thickness, hardness, drug content uniformity, friability, in-vitro drug release studies and release kinetic studies were performed. All the evaluation parameters results were significant. In-vitro drug release studies were performed and drug release kinetics evaluated using the linear regression method was found to follow Zero order, First order, Matrix and Korsemeyer and Peppas' equation. The prepared formulation shows better and significant results for all the evaluated parameters. The formulation A7 shows maximum percentage of drug release (99.45%) and prolonged release for time period of about 12h, there by improves the bioavailability and patient compliance.

Keywords: *Apremilast, HPMC K 15,Sodium CMC and Guar Gum*

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INTRODUCTION:

Oral drug delivery has been known for decades as the most widely utilized route of administered among all the routes that have been employed for the systemic delivery of drug via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration belief that by oral administration of the drug is well absorbed. All the pharmaceutical products formulated for systemic delivery via the oral route of administration irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage forms (either solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology, pharmacokinetics, pharmacodymics and formulation design is essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form. [1,2]

Sustained drug delivery system:

Over the past 30 years, as the expense and complication involved in marketing new entities have increased with concomitant recognition of the therapeutics advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled drug delivery system. Sustained release technology is relatively new field and as a consequence, research in the field has been extremely fertile and has produced many discoveries. With many drugs, the basic goal is to achieve a steady state blood level that is therapeutically effective and non-toxic fir an extended period of time. The design of proper dosage form is an important element to accomplish this goal. Sustained release, sustained action, prolonged action, controlled release, extended action, timed release and depot dosage form are term used to identify drug delivery system that are designed to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after adminisatration of a single dose. In the case of oral sustained released dosage form, an effect is for several hours depending upon residence time of formulation in the GIT.

Physician can achieve several desirable therapeutics advantages by prescribing sustained release dosage form. Since, the frequency of drug administration is reduced, patient's compliances can be improved and the drug administration can be made more convenient as well. The blood level oscillation characteristics of multiple dosing form of conventional dosage form is reduced, because more even blood level is maintained in the design of sustained release dosage form. The total amount of drug administered, thus maximum availability with a minimum dose. In addition, the safety margin of high potency drug can be increased and the incidence of both local and systemic adverse effects can be reduced in sensitive patients. Overall, increased administration of sustained release dosage form gives increased reliability.

Not all the drugs are the suitable candidates for the sustained release dosage form. Ideal characteristic of the drug for the sustained release dosage form are;

- Drug should have a shorter half-life as drug with a longer half-life are inherently long acting drugs.
- Drug should be absorbed from large portion of gastrointestinal tract, since absorption must occur through the gut.
- Drug should be having a good solubility profile to be a good candidate for sustained release dosage form.
- Dose of the drug should not be too large, as a larger dose is to be incorporated into sustained release dosage form. [3,4,5]

Recent trends in sustained drug delivery system:

Sustained release dosage forms are categorized as:

- Single unit dosage form.
- Multiple unit dosage form.
- Mucoadhesive system.

Single unit dosage form:

These refer to diffusion system where the drug is uniformly distributed (dispersed / dissolved) throughout the solid matrix and the release of the drug is controlled or sustained either by incorporating hydrophilic or hydrophobic filler within the matrix or by coating the drug matrix with a swellable or non-swellable polymer film.

These systems can be classified as:

Monolithic system:

If the release rate is controlled or sustained by incorporating hydrophilic or hydrophobic filler within the matrix then the system is called as Monolithic device where the diffusion of drug through the matrix is rate- limiting step.

These are categorized as:

Hydrophobic/Swellable tablet:

Tablet prepared by mixing the drug with hydrophobic/hydrophilic filler appear to extend the release time of the drug from device within the GI tract after oral administration.

Floating tablet or capsule:

Designing of Floating tablet or capsule are called hydro-dynamically balanced drug delivery system is

based on the principle that device with gravity lesser than that of the gastric juice of stomach and retain the drug in the proximal region of the GIT.

Semisolid matrix system:
In this system, the hydrophobic carrier occurs in an oily semisolid state where the drug is incorporated and the final mass is usually filled into gelatin capsule to prepare the dosage form.

Coated tablet and Similar Multilayer system:
Multilayer systems are designed in such a way that the drug has to cross a barrier or membrane on its way from the device to the physiological environment. The nature and the number of barriers control the release process. In the simplest form coated tablet comprised a core containing the drug and a coating layer, which surrounds the core. The core is usually the drug either alone or loaded on to an inert material (hydrophilic or hydrophobic).
Multilayered tablet having two or more distinct layers usually prepared by dry coating technique have also been used to formulate sustained or controlled preparations for water-soluble drugs. In this case, coating which controls the release process covers the core tablet containing the drug only partially.

Osmotic device:
In osmotic device usually an osmotic agent (often with an osmotic adjuvant) is contained within a rigid compartment that is separated from the osmotic compartment by a partition. In the physiological environment the aqueous fluid penetrates across the membrane and the increased volume within the osmotic compartment pushes the drug out of the device through a delivery orifice.

Multiple unit dosage forms:
It represents a combination of subnets of the dosage forms, the source of which may either be homogeneous or heterogeneous. It offers the advantages of releasing one of the drugs or part of the same drug immediately while remaining drug or parts of the same can be sustained release. These are useful where drug-excipients and drug-drug interactions are inevitable in a single unit dosage form .The various forms are as:

- Micro granules/Spheroids.
- Beads.
- Pellets.
- Microcapsules.

Mucoadhesive systems:
It utilizes principle of bioadhesion for optimum delivery of the drug from the device. Bioadhesion is definable as the occurrence in which one biological substance is adhered to another substance, which may either, be of biological or non-biological origin. If the substance is mucosal membrane the phenomenon is known as mucoadhesion. Conventional controlled release dosage forms described above are restrained localized in selected regions of GIT.Mucoaadhsive systems are suitable to increased the contact time of drug with absorbing membrane and localization of delivery of drug at target sites.[3]

MATRIX SYSTEM:
The matrix system is most often used for a drug-controlled release from a pharmaceutical dosage form. Among the innumerable method used in controlled release drug from pharmaceutical dosage form, the matrix system is the most frequently applied; it is release system for delay and control of the release of the drug that is dissolved or dispersed in a resistant supports to disintegration. To define matrix, it is necessary to know the characters that differentiate it from other controlled release dossage forms. Hence the following must be considered:
The chemical nature of support (generally, the support are formed by polymeric net)

- ✓ The physical state of drug (dispersed under molecular or particulate form or both)
- ✓ The matrix shape and alteration in volume as a function of time.
- ✓ The route of administration (oral administration remains the most widely used but other route are adaptable)
- ✓ The release kinetic model.

ADVANTAGES OF MATRIX SYSTEM:
1.The interest awakened by matrix system in last few years is completely justified in view of the major advantages. Among these, the following stand out.
2.With proper control of manufacturing process, reproducible release profiles are possible.
3.There is no risk of "dumping" of a large part of dose, through the structure makes the immediate release of a small amount of active principle unavoidable.
4. Their capacity to incorporate active principle is large, which suits them to delivery of large dosage.[6]

The Following are the Rationale of Developing SR Matrix DDS To extend the duration of action of the drug

- ✓ To reduce the frequency of dosing
- ✓ To minimize the fluctuations in plasma
- ✓ level Improved drug utilization
- ✓ Less adverse effects

Advantages of SR Matrix DDS:

- The frequency of drug administration is reduced.
- Patient compliance can be improved.
- Drug administration can be made more convenient as well.
- The blood level oscillation characteristic of multiple dosing of conventional dosage forms is reduced.
- Better control of drug absorption can be attained, since the high blood level peaks that may be observed after administration of a dose of a high availability drug can be reduced.
- The characteristic blood level variations due to multiple dosing of conventional dosage forms can be reduced.
- The total amount of drug administered can be reduced, thus:
- -Maximizing availability with minimum dose
- -Minimize or eliminate local side effects
- -Minimize or eliminate systemic side effects
- -Minimize drug accumulation with chronic dosing
- Safety margins of high potency drugs can be increased and the incidence of both local and systemic adverse side effects can be reduced in sensitive patients.
- Improve efficiency in treatment.
    - Cure or control condition more promptly
    - -Improve control of condition
    - -Improve bioavailability of some drugs
    - -Make use of special effects; e.g. sustain release aspirin for morning relief of arthritis by dosing before bed-time.
- Economy.

Disadvantages of SR matrix DDS:

- Probability of dose dumping.
- Reduced potential for dose adjustment.
- Cost of single unit higher than conventional dosage forms.
- Increase potential for first pass metabolism.
- Requirement for additional patient education for proper medication.
- Decreased systemic availability in comparison to immediate release conventional dosage forms.
- Poor in vitro and in vivo correlations.

MATERIALS AND METHODS:

Apremilast-Procured From Dr Reddy's drugs private limited, Hyderabad. Provided by SURA LABS, Dilsukhnagar, Hyderabad, HPMC K 15-S. D. Fine Chem. Labs. Mumbai, India, Sodium CMC-S. D. Fine Chem. Labs. Mumbai, Guar Gum-S. D. Fine Chem. Labs. Mumbai, PVPK30-S. D. Fine Chem. Labs. Mumbai, Talc-S. D. Fine Chem. Labs. Mumbai, Mg stearate-S. D. Fine Chem. Labs. Mumbai, MCC-S. D. Fine Chem. Labs. Mumbai

METHODOLOGY:

Analytical method development:

a) Determination of absorption maxima:

100mg of Apremilast pure drug was dissolved in 15 ml of Methanol and make up to 1000ml with 0.1N HCL (stock solution-1). 10ml of above solution was taken and make up with 100ml by using 0.1N HCL (stock solution -2 i.e 100µg/ml). From this 10 ml was taken and make up with 100 ml of 0.1 N HCL (10µg/ml). Scan the 10µg/ml using Double beam UV/VIS spectrophotometer in the range of 200-400nm.

b) Preparation calibration curve:

100mg of Apremilast pure drug was dissolved in 15ml of Methanol and volume make up to 100ml with 0.1N HCL (Stock solution-1). 10ml of above solution was taken and male up with 100ml by using 0.1N HCL (Stock solution-2 i.e 100µ/ml). From this take 0.5,1,1.5,2 and 2.5ml of solution and make up to 10 ml 0.1N HCL to obtain 5, 10, 15, 20, and 25µg/ml of Apremilast +per ml of solution. The absorbance of the above dilutions was measured at 229 nm by using UV-Spectrophotometer taking 0.1N HCL as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis Which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) Which determined by least-square linear regression analysis. The above was procedure was repeated by using pH 6.8 phosphate buffer solutions.

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy:

Drug excipient interaction studies are significant for the successful formulation of every dosage form. Fourier Transform Infrared (FTIR) Spectroscopy studies were used for the assessment of physicochemical compatibility and interactions, which helps in the prediction of interaction between drug and other excipients. In the current study 1:1 ratio was used for preparation of physical mixtures used for analyzing of compatibility studies. FT-IR studies were carried out with a Bruker, ATR FTIR facility using direct sample technique.

Formulation development of Sustained release Tablets:

All the formulations were prepared by Direct Compression Method. The compositions of different formulations are given in the Table. The tablets were prepared as per the procedure given below and aim is to prolong the release of Apremilast.

Procedure:

1) Apremilast and all other ingredients except PVP and Talc were individually passed through sieve no ≠ 40.
2) Apremilast, MCC, and polymer mix thoroughly than add the binder powder mix properly up to 15 min.
3) Dry the above mixture at 65-70ºC by using dryer
4) After completion of drying the mixture is passed through sieve no ≠ 22.
5) The powder mixture was lubricated with PVP and Talc
6) Finally go for compression.

Table : Formulation of Sustained release tablets

Ingredients	A1	A2	A3	A4	A5	A6	A7	A8	A9
Apremilast	30	30	30	30	30	30	30	30	30
HPMC K 15	15	30	45	-	-	-	-	-	-
Sodium CMC	-	-	-	15	30	45	-	-	-
Guar Gum	-	-	-	-	-	-	15	30	45
PVPK30	10	10	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5	5	5
Mg stearate	5	5	5	5	5	5	5	5	5
MCC	85	70	55	85	70	55	85	70	55
Total weight	150	150	150	150	150	150	150	150	150

RESULT AND DISCUSSION:

The present work was designed to develop sustained tablets of Apremilast using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

Analytical Method:

Standard graph of Apremilast in 0.1N HCL:

The scanning of the 10 µg/ml solution of Apremilast in the ultraviolet range (200-400nm) against 0.1 N HCL the maximum peak observed at λ_{max} as 229 nm. The standard concentration of Apremilast (5-25µg/ml) was prepared in 0.1N HCL showed good linearity with R^2 value of 0.999, which suggests that it obeys the Beer-Lamberts law.

Table : Standard curve of Apremilast 0.1N HCL

Concentration(µg/ mL)	Absorbance
0	0
5	0.106
10	0.211
15	0.318
20	0.413
25	0.517

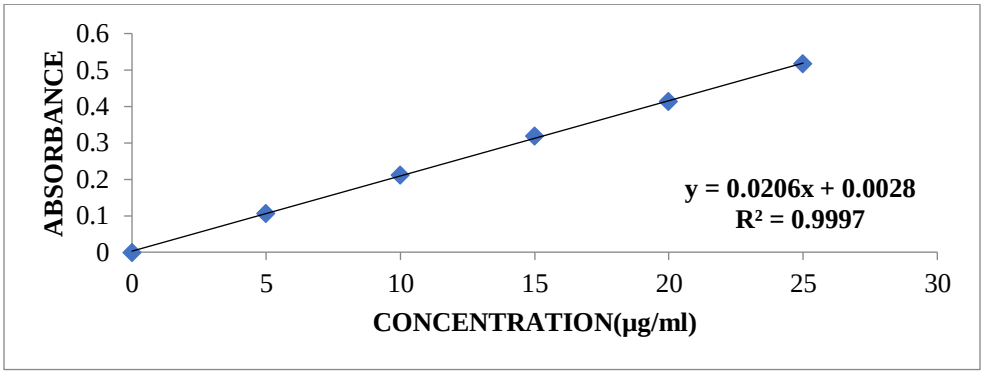

Fig : Calibration curve of Apremilast 0.1N HC1 at 229 nm

Standard Curve of Apremilast Phosphate buffer pH 6.8:

The scanning of the 10 µg/ml solution of Apremilast the ultraviolet range (200-400nm) against 6.8 pH phosphate the maximum peak observed at the λ_{max} as 229 nm. The standard concentrations of Apremilast (5 -25µg/ml) prepared in 6.8 pH phosphate buffer showed good linearity with R^2 value of 0.997, which suggests that it obeys the Beer-Lamberts law

Table : Standard curve of Apremilast buffer pH 6.8

Concentration (µg / ml)	Absorbance
0	0
5	0.137
10	0.266
15	0.389
20	0.515
25	0.644

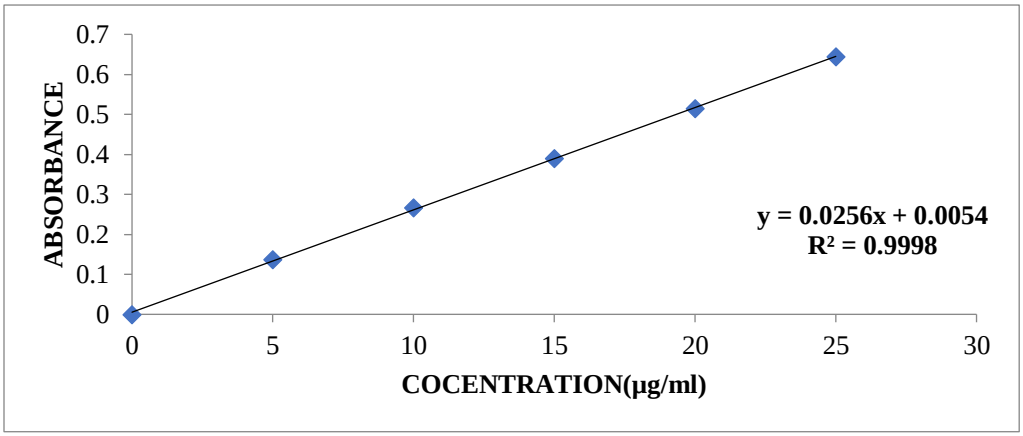

Fig.8.2: Calibration of Apremilast Phosphate buffer pH 6.8

Drug and Excipient Compatibility Studies:

FTIR study:

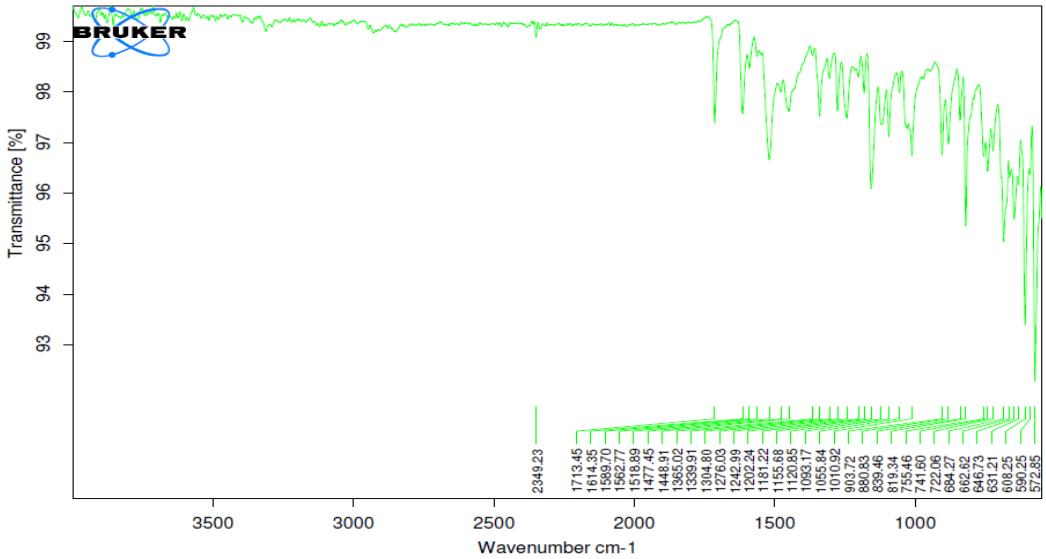

Fig: FTIR graph of pure drug

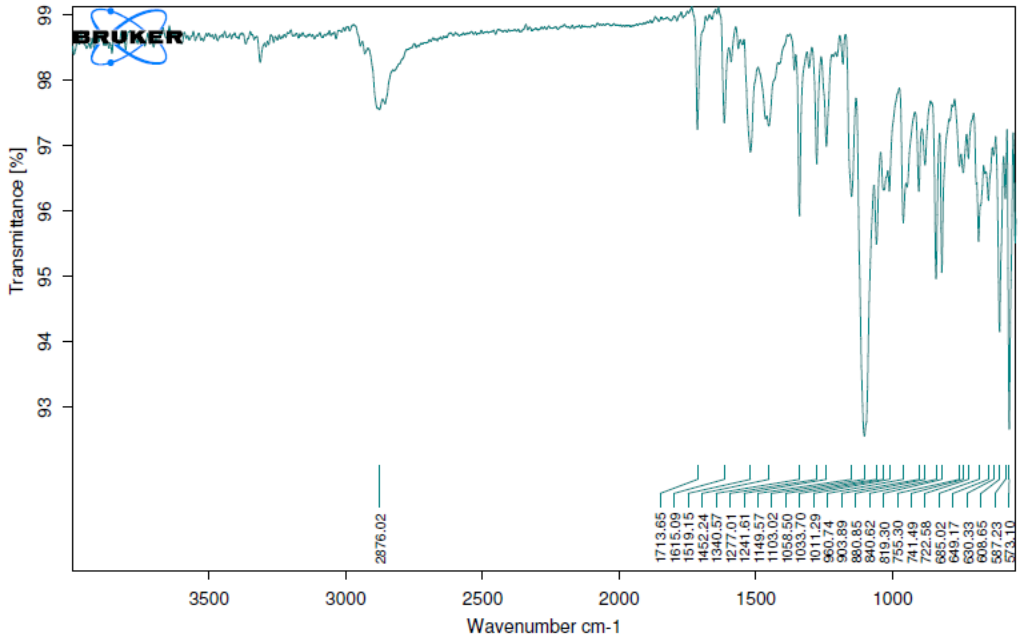

Fig: FTIR graph of optimized formulation

From the FTIR data is was evident that the drug and excipient does not have any interactions. Hence they were compatible.

EVALUATION PARAMETERS:

Pre-compression parameters

Table: Pre-compression parameters of powder blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
A1	25.5±0.86	0.15±0.02	0.17±0.02	11.8±0.45	1.14±0.05
A2	24.4±0.79	0.16±0.01	0.19±0.01	14.3±0.65	1.18±0.02
A3	22.4±0.79	0.15±0.03	0.18±0.03	16.4±0.91	1.20±0.01
A4	25.6±0.79	0.16±0.03	0.20±0.02	20.2±0.97	1.23±0.07
A5	26.9±0.55	0.15±0.02	0.17±0.02	11.9±0.67	1.13±0.03
A6	25.7±0.6	0.13±0.01	0.15±0.01	12.3±0.96	1.14±0.03
A7	24.7±1.05	0.14±0.03	0.17±0.02	20.1±0.90	1.12±0.02
A8	25.5±0.83	0.16±0.02	0.18±0.03	11.3±0.73	1.12±0.01
A9	27.3±1.25	0.17±0.02	0.21±0.01	15.2±1.11	1.17±0.02

Tablet powder blend was subjected to various pre-compression parameters. The angle of repose values was showed from 22.4±0.79 to 27.3±1.25; it indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.13±0.01 to 0.17±0.02 (gm/cm^3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.15±0.01 to 0.21±0.01 showing he powder has good flow properties. The compressibility index of all the formulations was found to ranging from 11.3±0.73 to 20.2±0.97 which showed that the powder has good flow properties. All the formulations were showed the Hausner ratio ranging from 1.12±0.01 to 1.23±0.07 indicating the powder has good flow properties.

Post Compression Parameters For Tablets:

Table: Post compression parameters of tablets

Formulation codes	Average Weight (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
A1	148.35	2.53	0.58	1.85	99.33
A2	149.48	2.69	0.63	1.74	98.25
A3	151.08	1.89	0.44	2.35	98.63
A4	147.13	2.37	0.52	1.96	97.17
A5	152.86	2.43	0.47	1.53	98.74
A6	148.22	2.92	0.36	2.44	99.35
A7	150.46	1.76	0.29	1.22	99.67
A8	151.38	2.68	0.38	1.67	98.08
A9	149.24	1.94	0.41	1.59	97.23

Weight variation and Thickness :
All the formulations were evaluated for uniformity of weight using electronic weighing balance and the results are shown in table .The average tablet weight of all the formulations was found to be between 148.22 to 150.46 mg. The maximum allowed percentage weight variation for tablets weighing >150 mg is 5% and no formulations are not exceeding this limit. Thus all the formulations were found to comply with the standards given in I.P and thickness of all the formulations was also complying with the standards that were found to be between1.53 to 2.44.

Hardness and Friability:
all the formulations were evaluated for their hardness, using Monsanto hardness tester and the results are shown in table. The average hardness for all the formulations was found to be between(1.76 to 2.92) kg/cm^2 which was found to be acceptable.

Friability was determined to estimate the ability of the tablets to withstand the abrasion during packing, handling and transporting. All the formulations were evaluated for their percentage friability using Roche friabilator and the results were shown in table .The average percentage friability for all the formulations was between 0.29 to 0.63, which was found to be within the limit .

Drug content:
All the formulations were evaluated for drug content according to the procedure described in the methodology section and the results were shown in table. The drug content values for all the formulations were found to in range of (97.17 to 99.67). According to IP standards the tablets must contain not less than 95% and not more than 105% of the stated amount of the drug. Thus, all the FDT formulations comply with the standards given in IP.

***In vitro* drug release studies:**
The formulations prepared with different polymers by direct compression method. The tablets dissolution study was carried out in paddle dissolution apparatus using 0.1 N HCL for 2 hr and 6.8 pH phosphate buffer for remaining hours as a dissolution medium

Table : Dissolution Data of Apremilast Tablets

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED								
	A1	A2	A3	A4	A5	A6	A7	A8	A9
0	0	0	0	0	0	0	0	0	0
1	9.17	11.65	9.25	12.51	9.49	8.72	11.41	9.27	11.56
2	18.62	14.58	21.41	19.25	17.25	15.67	15.65	12.81	17.43
3	26.69	21.41	28.29	29.76	21.45	31.82	26.39	22.72	28.34
4	31.85	27.65	39.36	38.36	25.31	39.46	38.53	28.63	37.58
5	37.76	32.64	46.52	45.93	35.42	51.17	44.27	41.97	44.36
6	46.45	43.12	61.25	54.46	49.51	55.27	53.72	52.51	51.77
7	51.54	48.25	69.55	63.26	53.35	71.63	64.19	63.44	62.65
8	57.37	61.37	71.42	71.55	62.68	73.33	75.22	72.25	73.51
9	64.66	69.54	76.37	75.38	75.59	82.64	84.81	81.49	77.72
10	71.82	74.48	82.36	81.72	81.47	89.67	88.42	85.78	81.49
11	81.17	82.66	85.59	85.89	87.35	91.58	92.47	89.23	86.18
12	86.55	86.72	91.85	91.43	92.26	94.69	99.45	95.79	94.71

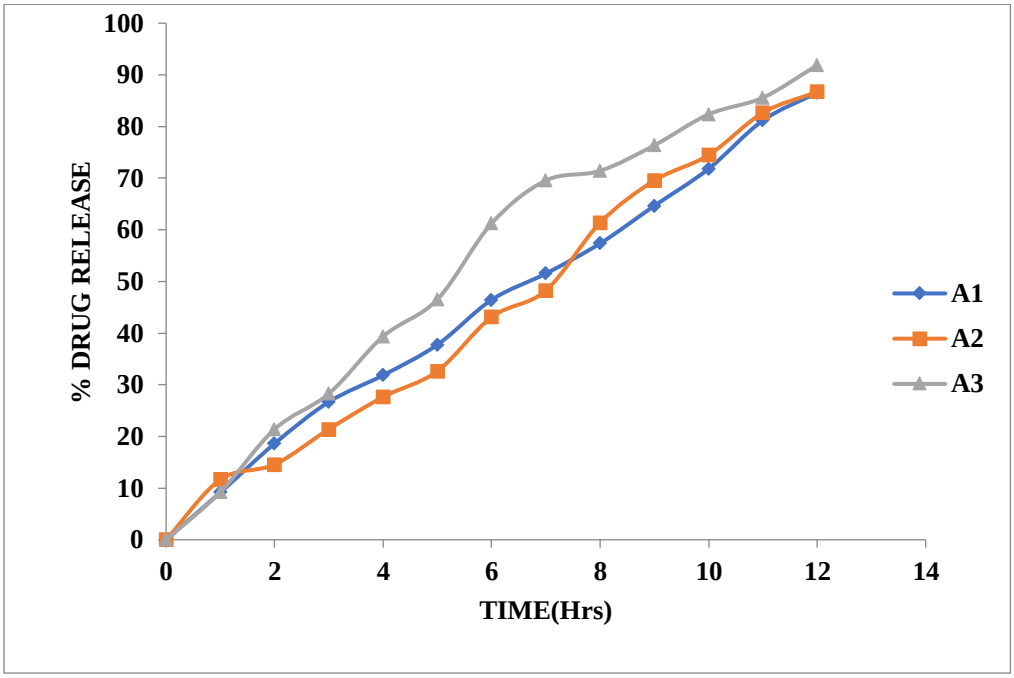

Figure :Dissolution study of Apremilast Sustained Release tablets (A1 to A3)

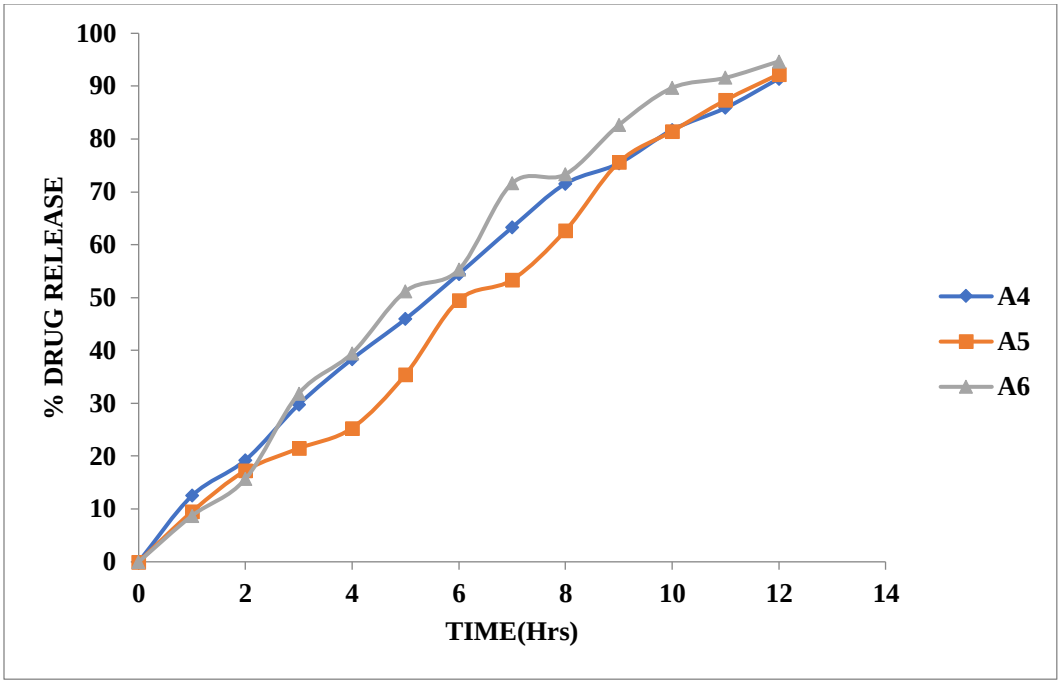

Figure: Dissolution study of Apremilast tablets (A4 to A6)

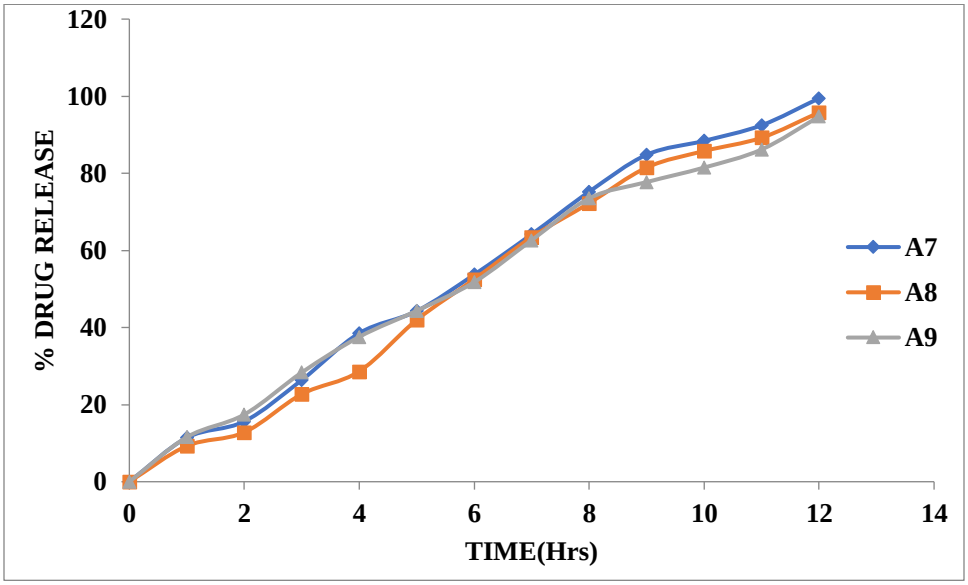

Figure : Dissolution study of Apremilast tablets (A7-A9)

Formulations prepared with HPMC K 15 retarded the drug release in the concentration of 45 mg (A3Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 91.85% in 12 hours with good drug release.

Whereas the formulations prepared with Sodium CMC were retarded the drug release in the concentration of 45 mg (A6Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 94.69% in 12 hours with good retardation.

Whereas the formulations prepared with Guar Gum were retarded the drug release in the concentration of 15 mg (A7Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 99.45% in 12 hours with good retardation.

Among all the formulations A7 formulation containing (Drug: Guar Gum) 1:3 ratio showed maximum % drug release i.e. 99.45% at 12 hr.

Hence based on dissolution data of 9 formulations, A7 formulation showed better release up to 12 hours. So A7 formulation is optimized formulation,

Application Of Release Rate Kinetics To Dissolution Data

Data of *in vitro* release studies of formulations which were showing better drug release were fit into different equations to explain the release kinetics of Apremilast release from sustained tablets. The data was fitted into various kinetic models such as zero, first order kinetics ,Higuchi and Korsmeyer peppas mechanisms and the results were shown in the below table .

Table : Release Kinetics data for optimized formulation (F7)

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG (%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
11.41	1	1.000	1.057	0.000	1.947	11.410	0.0876	-0.943	88.59	4.642	4.458	0.184
15.65	2	1.414	1.195	0.301	1.926	7.825	0.0639	-0.805	84.35	4.642	4.386	0.256
26.39	3	1.732	1.421	0.477	1.867	8.797	0.0379	-0.579	73.61	4.642	4.191	0.451
38.53	4	2.000	1.586	0.602	1.789	9.633	0.0260	-0.414	61.47	4.642	3.947	0.695
44.27	5	2.236	1.646	0.699	1.746	8.854	0.0226	-0.354	55.73	4.642	3.820	0.822
53.72	6	2.449	1.730	0.778	1.665	8.953	0.0186	-0.270	46.28	4.642	3.590	1.051
64.19	7	2.646	1.807	0.845	1.554	9.170	0.0156	-0.193	35.81	4.642	3.296	1.345
75.22	8	2.828	1.876	0.903	1.394	9.403	0.0133	-0.124	24.78	4.642	2.915	1.726
84.81	9	3.000	1.928	0.954	1.182	9.423	0.0118	-0.072	15.19	4.642	2.477	2.165
88.42	10	3.162	1.947	1.000	1.064	8.842	0.0113	-0.053	11.58	4.642	2.262	2.379
92.47	11	3.317	1.966	1.041	0.877	8.406	0.0108	-0.034	7.53	4.642	1.960	2.682
99.45	12	3.464	1.998	1.079	-0.260	8.288	0.0101	-0.002	0.55	4.642	0.819	3.822

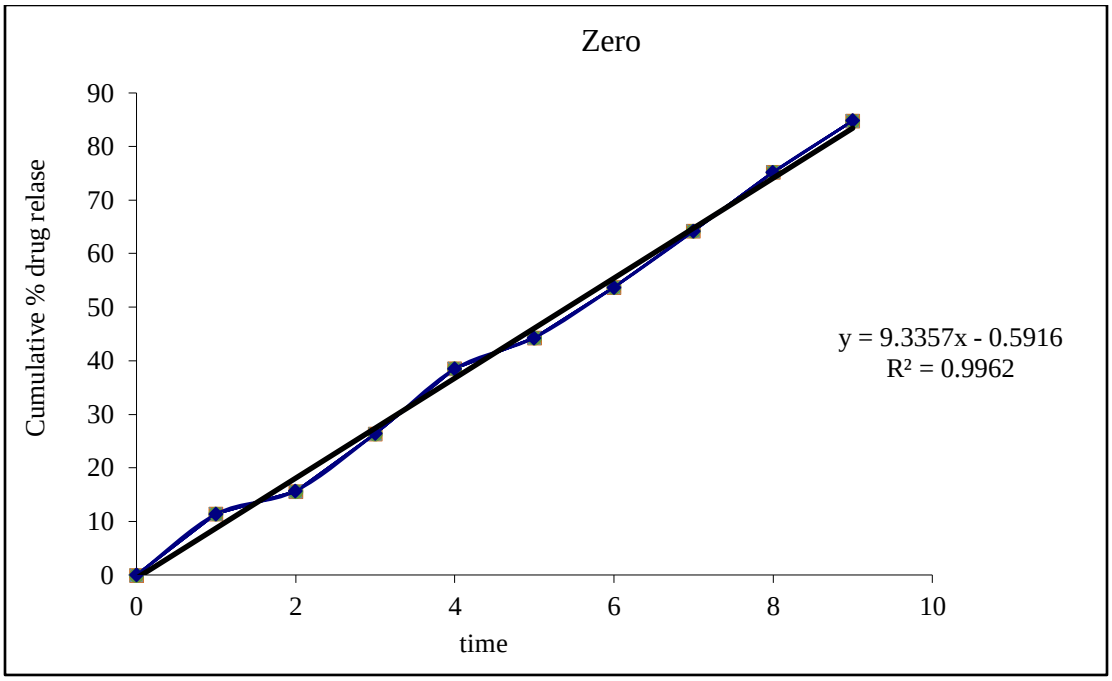

Figure : Graph of zero order kinetics

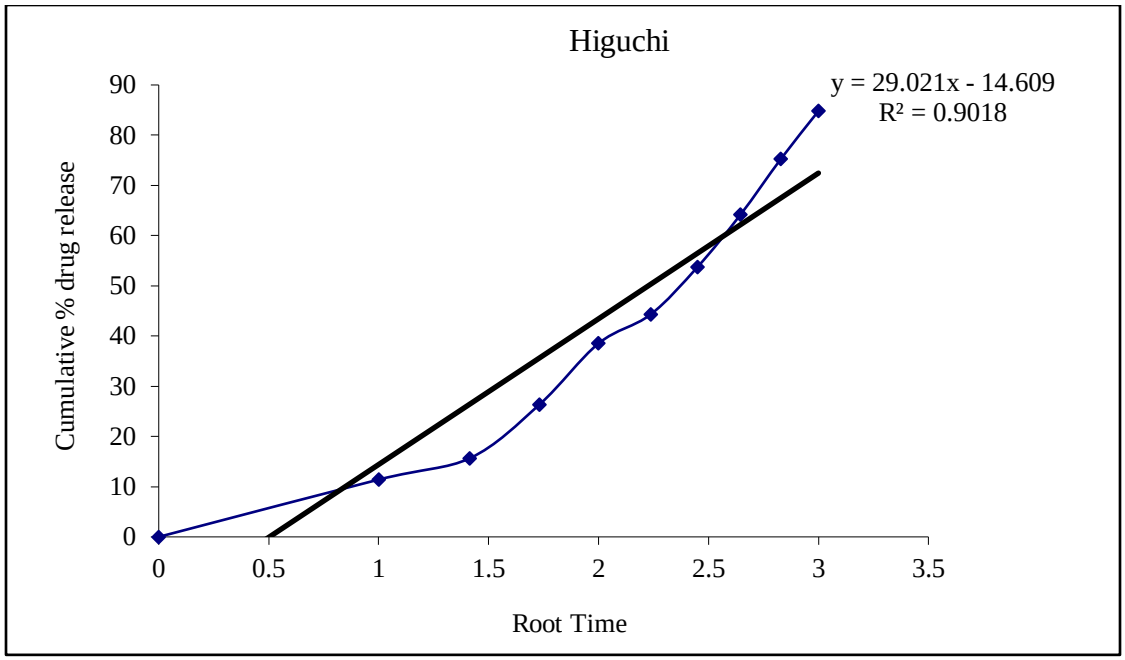

Figure: Graph of Higuchi release kinetics

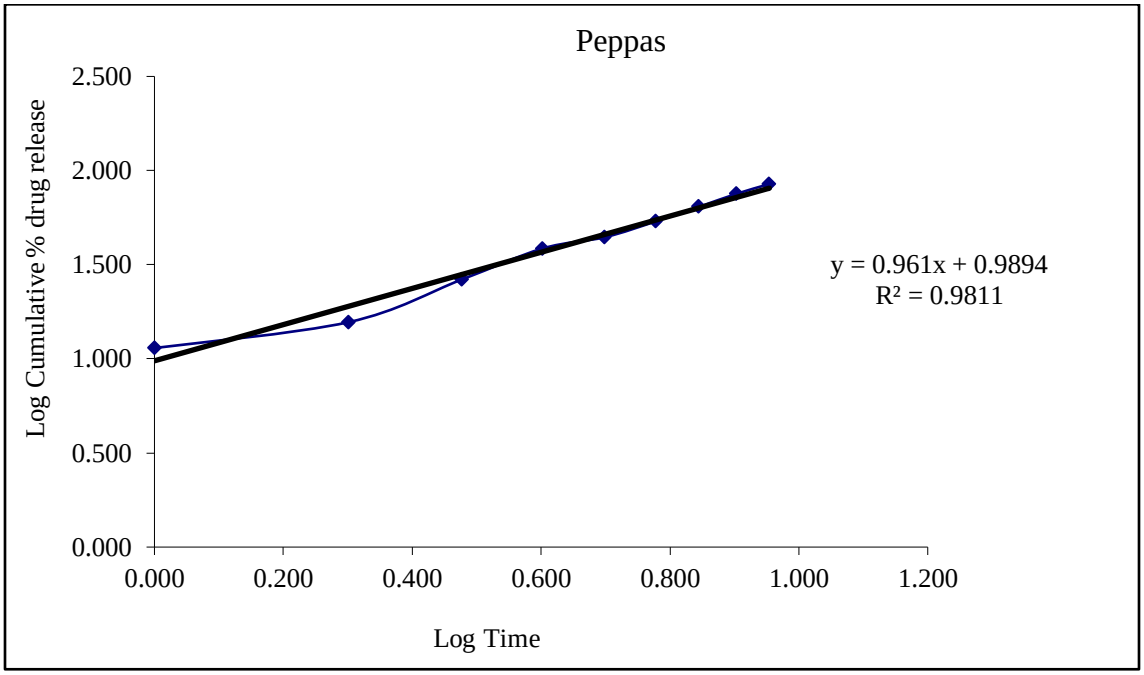

Figure : Graph of peppas release kinetics

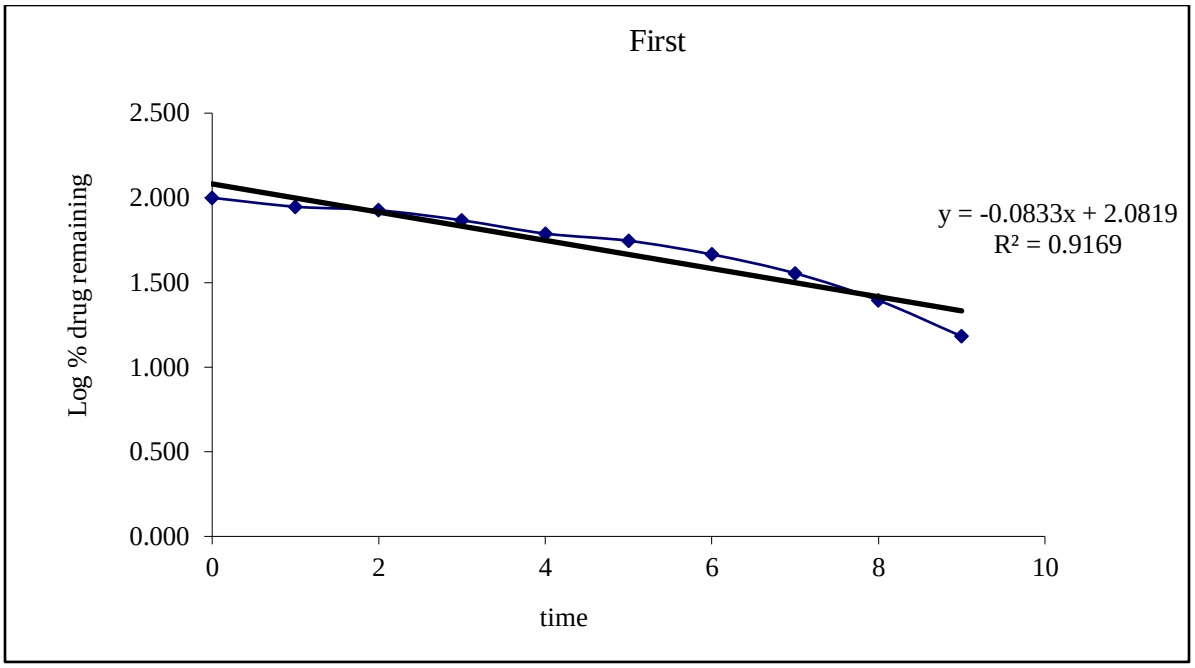

Figure: Graph of first order release kinetics

Based on the data above results the optimized formulation followed zero order release kinetics.

CONCLUSION:

The present work is formulate and evaluate of sustained release tablets of Apremilast drug. The main aim of this research work is to develop sustained release tablets of Apremilast view to prolong the drug release and to give to the action of drug for long duration and to avoid noncompliance of it. *In vitro* of sustained release tablets for the batch A7 was found to be 99.45% .From over all observations and study physical properties. *In vitro* study its complies with the IP standard for sustained release dosage form tablet of A7 batch was consider as optimized formulation.

Optimized formulation indicate that there were no significant changes in drug content as well as dissolution parameters. The advantages of sustained release tablets is to extended the release drug and prolong its action. The sustained release tablet formulation can reduce dosing frequency decrease side effect and improve patient compliance.

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