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DEVELOPMENT AND EVALUATION OF APREMILAST NANOSUPENSION FOR ORAL DRUG DELIVERY SYSTEM

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ABSTRACT

The oral bioavailability of poorly water soluble drug can be enhanced using nanosuspension. Nanosuspensions are colloidal dispersion of uniform-sized solid particles dispersed in an aqueous vehicle. The present work is aimed at the development and evaluation of nanosuspension of apremilast, a poorly water soluble antipsoratic drug. The nanosuspension of apremilast may enhance the dissolution rate of drug to improve its oral bioavailability. The nanosuspensions were prepared by using high pressure homogenization. The prepared nanosuspensions were evaluated for particle size, zeta potential, polydispersity index. The effect of variable concentration of drug and stabilizer and solvent to antisolvent ratio on the physical, morphological and dissolution properties of apremilast were studied. The average particle size of apremilast nanoparticles was found to be in the range of 399 nm. The particle size varies with increase in concentration of drug and stabiliser. The nanosuspension showed negative zeta potential i.e. about -14.1. The dissolution profiles of nanosuspension formulation showed up to 98.34% release in 6 h. The prepared nanosuspension showed enhanced dissolution which may lead to enhanced oral bioavailability of apremilast.

KEYWORDS

Nanosuspension, Apremilast, Solubility and Drug.

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INTRODUCTON

Psoriasis is regarded as an autoimmune disease in which genetic and environmental factors have a important role. The name of the disease is comes from Greek word “psora” which means “itch”. Psoriasis is a non-contagious, dry, inflammatory and dreadful skin disorder, which can involve total system of person. It is mostly inherited and mainly characterized by sharply marginated scaly,

erythematous plaques that develop in a relatively symmetrical distribution. The disease commonly affects sites such as scalp, tips of fingers and toes, palms, soles, umbilicus, gluteus, under the breasts and genitals, elbows, knees, shins and sacrum[1].

In recent years, research in the field of nanotechnology and its applications in drug delivery has gained a momentum. They were identified to be a promising drug delivery systems for a wide range of drugs having low molecular weight to macromolecules, peptides, proteins or genetic materials targeted to particular cells or tissues. Nanoparticles are also preferred for their improved bioavailability and stability of drug molecules against enzymatic degradation[2]. Nanosuspensions are colloidal dispersions of nanosized drug particles which are stabilized by surfactants. They can also be defined as a biphasic system consisting of pure drug particles dispersed in an aqueous vehicle in which suspended particle have diameter less than 1μm in size. Reduction of drug particles to nanometer range leads to an enhanced dissolution rate not only because of increased surface area but also because of saturation solubility[3].

Psoriasis and psoriatic arthritis are a chronic skin disease of autoimmune system that is identified as patches of abnormal skin. Apremilast inhibits the enzyme phosphodiesterase 4 which leads to spontaneous inhibition of tumor necrosis factor-alpha production from human rheumatoid synovial cell. In addition, the application of oral drug delivery has numerous problems such as abdominal pains, upper respiratory, nasopharyngitis, and depression that often ends in lack of patient compliance[4].

Apremilast is a novel PDE4 (4 phosphodiesterase) and TNF-α (tumor necrosis factor-alpha) inhibitor that was recently approved by FDA as a solid oral dosage form (tablet) for the treatment of skin psoriasis[5].

MATERIAL AND METHODS

Materials

Apremilast (Gift sample by Glenmark Pharmaceuticals, Sinnar, Nashik), It is a water-insoluble drug, so it is chosen as a main drug. Polyvinyl pyrrolidone was used as a polymer (Thomas Baker chemicals, Pvt Ltd, Mumbai.). Sodium lauryl sulphate is used as a surfactant (Reliance Cellulose, Mumbai). Triethanolamine used as a pH adjuster (Lobachemie Pvt. Ltd. Mumbai), Methyl paraben used as a preservative (Research lab fine Chem, industries, Mumbai).

Methods

High pressure homogenization (HPH)

For batch size 100 ml

Step 1

Accurate quantity of sodium lauryl sulphate and polyvinyl pyrrolidone was weighed and dissolved in water.

Step 2

Accurate quantity of apremilast was weighed and dissolved in 10ml acetonitrile as solvent.

Step 3

Solution prepared in step 1 can be mixed using high pressure homogenizer at about 8000 rpm.

Step 4

Add solution prepared in step 2 slowly with the help of syringe in mixture prepared in acetonitrile by heating.

Step 5

Using high pressure homogenizer at speed 15,000 rpm for 20 min nanosuspension was prepared.

Step 6

Addition of triethanolamine and methyl paraben to step 5 under homogenization[6].

EVALUATION PARAMETERS

Evaluation of Nanosuspension[7-12]

The Apremilast nanosuspension was evaluated for following parameters.

Physical appearance

The prepared apremilast nanosuspensions were inspected visually for their color, homogeneity, consistency.

Determination of pH

pH of all formulations was determined by using pH meter (DIGITAL pH METER). A 10% dispersion of formulation was prepared in distilled water and pH was determined by using pH meter which was previous standardized with standard buffers of pH.

Specific Gravity

Specific gravity bottle is used to check the density of the prepared formulation and in turn compared with the density of water. Weight of empty gravity bottle is taken as (M1), weight of specific gravity bottle containing the preparation is considered as (m2), weight of gravity bottle containing water is taken as (M3). Considering this data we can find,

Weight of preparation

(M1-M2)

Weight of purified water

(M3-M1)

$$\text{Specific gravity} = \frac{weight\ of\ preparation}{weight\ of\ an\ equal\ volume\ of\ water}$$

Particle size measurement

Particle size distribution of nanosuspension can be determined by photon correlation spectroscopy that analyzes fluctuations in light scattering due to Brownian motion of the particles, using Zetasizer 1000 HS [Malvern Instruments, UK].

Poly- dispersity index and zeta potential

The average diameters and polydispersity index of samples were measured by Photon Correlation Spectroscopy. The measurements should be performed at 25ºC.

Viscosity

The Viscosities of nanosuspensions were measured using a Brookfield rotational viscometer (LV2, Brookfield Inc., USA). The viscosities of all the nanosuspensions were measured at 25ºC at 12 rpm using small volume adapter with Spindle S-18 and in triplicate.

Drug content determination

Drug concentration in nanosuspension of apremilast was measured by spectrophotometer. Apremilast content in nanosuspension was measure and added with known quantity of solvent [acetonitrile] and it get miscible. Absorbance was measured after suitable dilution at 229nm in UV/VIS spectrophotometer [Schimadzu 1800] and % drug content was calculated.

***In- Vitro* dissolution study**

In-vitro dissolution test was performed in USP apparatus type II using paddle method at rotation speed of 100rpm. Dissolution was carried out in 900ml phosphate buffer having pH 6.8 as a dissolution medium and temperature maintained at 37± 0.5º. Accurately weighed bulk drug and nanosuspensions were dispersed in dissolution medium; 5ml aliquots were removed at predertmined time intervals 1, 2, 3, 4, 5, 6 hrs. From dissolution medium and replace it with same buffer solution for maintained sink conditions and the sample were analyzed for the drug release using UV spectrophotometer at 229nm

Drug release kinetic study

To study the kinetics of in vivo drug release, data was applied to kinetic models such as zero order, first order, Higuchi and Connors model and Korsemeyer-Peppas. For zero order plot a graph % drug release Vs time, For first order plot a graph of log % cumulative drug remaining Vs time, For Higuchi-connors model % drug release Vs time and for Korsemeyer-Peppas Plot a graoh of log % drug release Vs time in log.

Stability studies

Nanosuspension formulations were subjected to stability studies as per ICH guidelines. Various parameters such as Physical appearance, drug content, temperature, humidity were measured before and after 30, 60 and 90 days of stability.

RESULTS

FTIR of pure drug and with excipients

FTIR o pure drug and drug with excipients was shown in Figure No.1 and No.2. It was observed that apremilast was compatible with PVP and SLS was polymer.

Particle size measurement

Particle size of nanosupension was shown in Figure No.3 and it was found to be 399 also PDI was found to be 0.556.

Table No.1: Trial batches of apremilast nanosuspension formulation

S.No	Ingredients	Concentration [Drug: stabilizer]								
		1:20			1:10			1:1		
		F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
1	Drug (mg)	10	10	10	10	10	10	10	10	10
2	PVP (mg)	2.5	5	7.5	25	50	75	50	100	150
3	SLS (mg)	7.5	5	2.5	75	50	25	150	100	50
4	TEA (mg)	3	3	3	3	3	3	3	3	3
5	Methyl paraben (mg)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
6	Acetonitrile (ml)	10	10	10	10	10	10	10	10	10
7	Dist. Water (ml)	100	100	100	100	100	100	100	100	100

Table No.2: Trial batches of apremilast nanosuspension formulation

S.No	Ingredients	Concentration [Drug: stabilizer]					
		1:40			1:30		
		F_{10}	F_{11}	F_{12}	F_{13}	F_{14}	F_{15}
1	Drug (mg)	10	10	10	10	10	10
2	PVP (mg)	75	150	225	100	200	300
3	SLS (mg)	225	150	75	300	250	100
4	TEA (mg)	3	3	3	3	3	3
5	Methyl paraben (mg)	0.5	0.5	0.5	0.5	0.5	0.5
6	Acetonitrile (ml)	10	10	10	10	10	10
7	Dist. Water (ml)	100	100	100	100	100	100

Table No.3: Condition for stability study

Duration of study	90 days
Temperature conditions	40ºC± 2ºC
Relative humidity conditions	75%±5%

***In-vitro* dissolution study**

Table No.4: Dissolution study of apremilast nanosuspension

Time [hrs]	% Release ± SD [FF3]
1	15 ± 0.85
2	40.20 ± 0.81
3	51.77 ± 0.88
4	68.34 ± 1.24
5	80.45 ± 0.16
6	98.34 ± 1.15

Dissolution Kinetics

Kinetic study

S.No	Release Kinetics	Parameter	Value
1	Zero order release kinetics	R^2	0.9883
2	First order release kinetics	R^2	0.722
3	Higuchi and Connors model	R^2	0.991
4	Korsemeyer peppas release kinetics	R^2	0.978

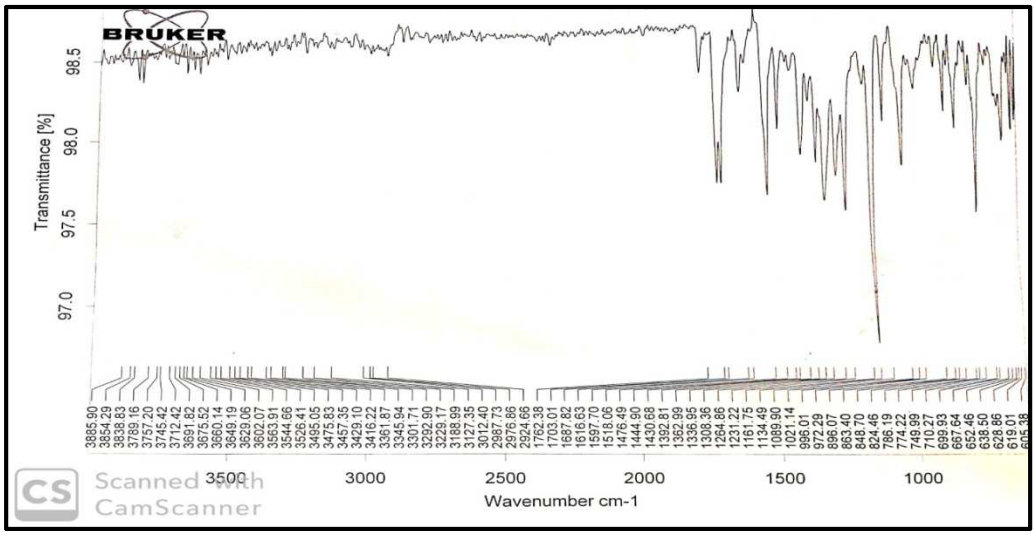

Figure No.1: The Infra-Red spectrum of Apremilast

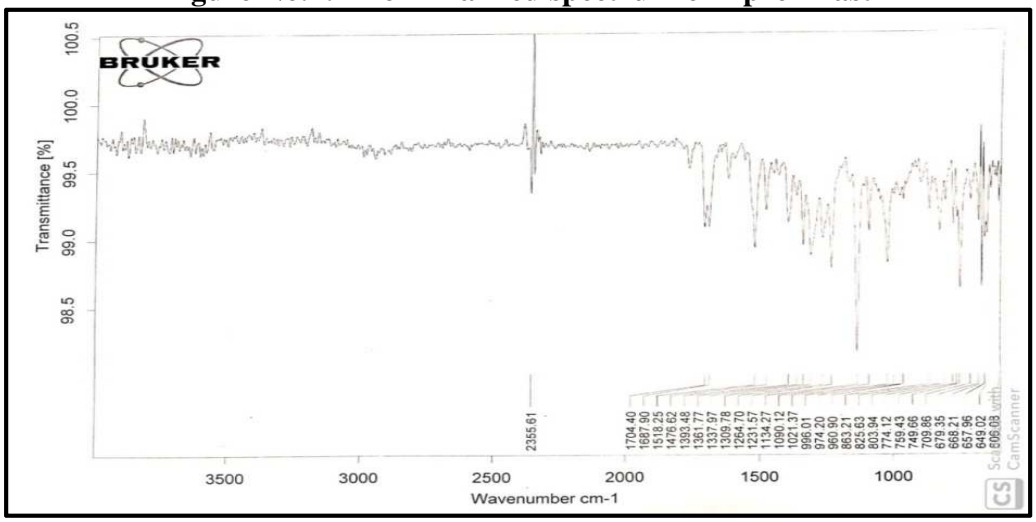

Figure No.2: FTIR of Apremilast with excipients

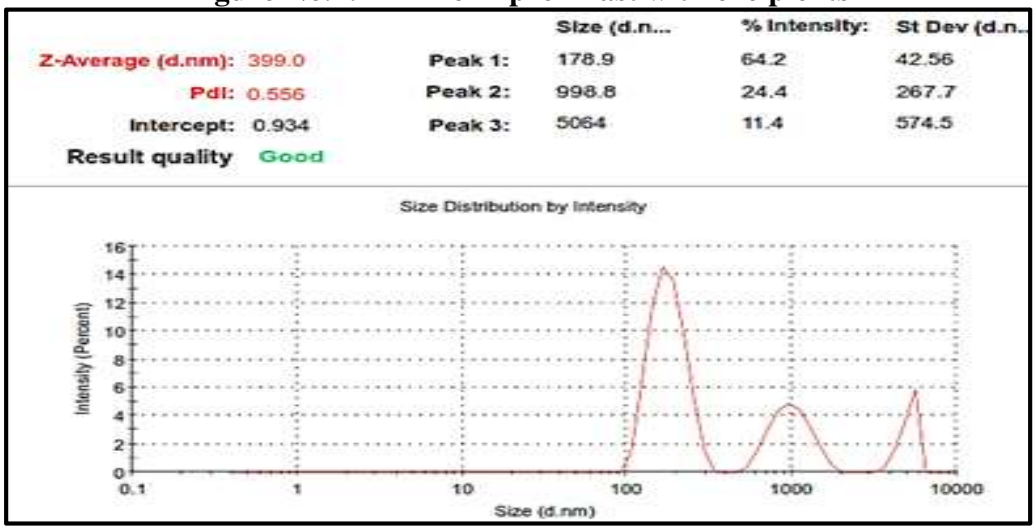

Figure No.3: Intensity of size distribution

Poly- dispersity index and zeta potential

Zeta potential of apremilast nanosuspension was found to be -14.1

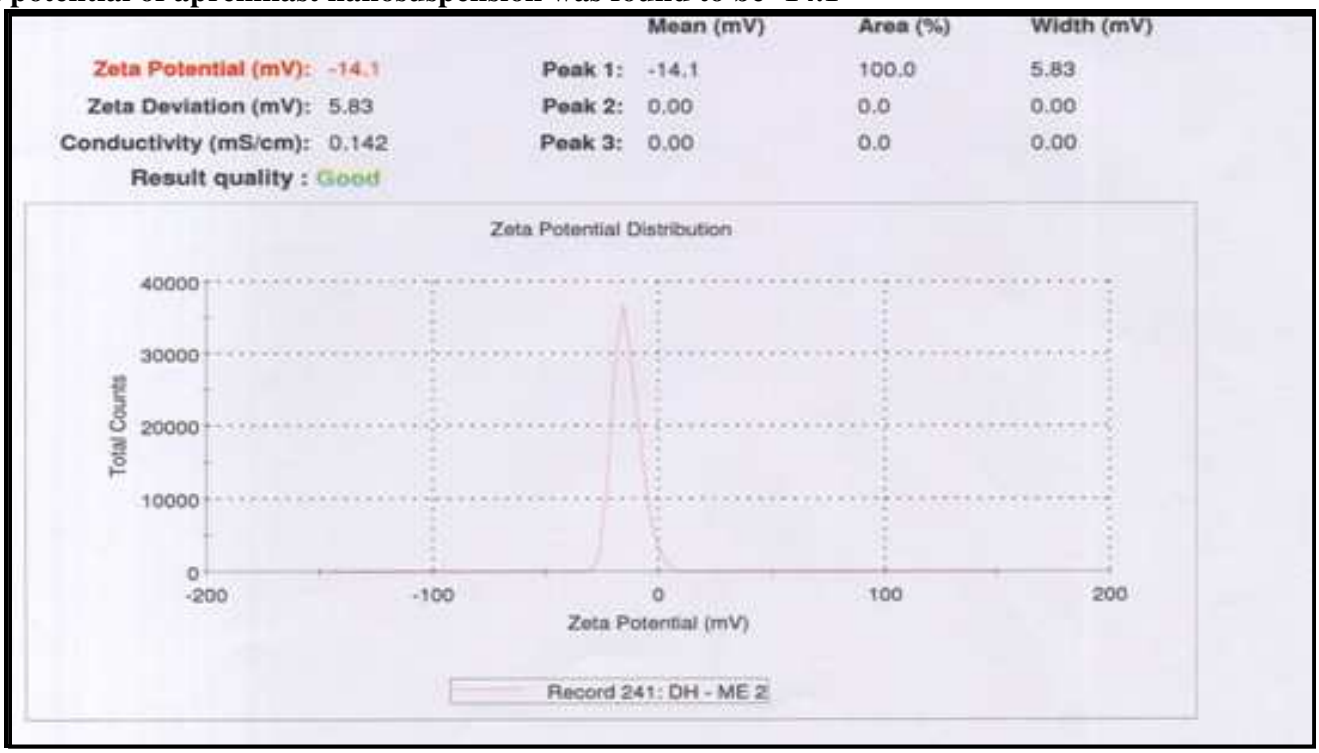

Figure No.3: Zeta potential distribution

SUMMARY AND CONCLUSION

The above investigations suggest the suitability of apremilast nanosuspension as a promising drug delivery system in the treatment of psoriasis. The comparison study of apremilast nanosuspension with marketed sustained release tablet also indicates that the dissolution of nanosuspension is higher than conventional preparation hence it can be very good alternative to the conventional therapy and alternative to the sustained release tablet formulation.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

BIBILIOGRAPHY

1. Ashwin B. Kuchekar, Rohini R. Pujari, Shantanu B. Kuchekar, Shashikant N. Dhole and Payal M. Mule. Psoriasis: A comprehensive review, *International Journal of Pharmacy and Life Sciences,* 2(6), 2011, 857-877.
2. Nilesh Jain, Ruchijain, Navneet Thakur, Brahmprakash Gupta, Deepak Kumar Jain, Jeethendra Banveer, Surendra Jain, *et al.* Nanotechnology: A Safe And Effective Drug Delivery System, *Asian Journal of Pharmaceutical and Clinical Research,* 3(3), 2010, 159-165.
3. Rupali L. Shid, Shashikant N. Dhole, Nilesh Kulkarni, Santosh L. Shid. Nanosuspension: A Review, *International Journal of Pharmaceutical Sciences Review and Research,* 22(1), 2013, 98-106.
4. Sai Priyanka N V. Formulation and Evaluation of gel loaded with Microspheres of Apremilast for Transdermal delivery

system, *Asian J Pharm Clin Res,* 12(2), 2019, 411-417.

5. Avadhesh Singh Kushwaha, Michael A. Repka and Narasimha Murthy S. A Novel Apremilast Nail Lacquer Formulation for the Treatment of Nail Psoriasis, *AAPS Pharm Sci Tech,* 18(8), 2017, 2949-2956.
6. Sunethra Kalvakuntla, Mangesh Deshpande, Zenab Attari, Koteshwara Kunnatur. Preparation and Characterization of Nanosuspension of Aprepitant by H96 Process, *Adv Pharm Bull,* 6(1), 2016, 83-90.
7. Willard H H, Merritt L L, Dean J A, Settle F A. Instrumental methods of analysis, *CBS Publishers and Distributors,* 7th Edition, 2004, 118-121, 287-320, 895.
8. Skoog D A, Holler F J, Crouch S R. Instrumental analysis, *Brooks Cole, Belmont, Australia,* 6th Edition, 2017, 411-436, 477-502.
9. Pavia D L, Lampman G M, Kriz G S, James R V. Spectroscopy, *Cennage learning PVT Ltd,* 9th Indian Edition, 2007, 38.
10. Faiyaz Shakeel, Nazrul Haq. Solubility and thermodynamics of apremilast in different mono solvents: Determination, correlation and molecular interactions, *International Journal of Pharmaceutics,* 523(1), 2017, 410-417.
11. Indian Pharmacopoeia. Government of India Ministry of Health and Family Welfare, *Published by the Indian Pharmacopoeia Commission Ghaziabad,* 1, 2007, 41, 179-180.
12. Meiqiong Tang, Ping Hu, Shigui Huang, Qiang Zheng, Hao Yu, and Yun He *et al.* Development of an extended-release formulation for apremilast and a level *in vitro-in vivo* correlation study in beagle dogs, *Chem. Pharma. Bull,* 64(11), 2016, 1607-1615.

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