Research Article

Design, Development and Characterization of Sustain Release Microsphere of Apremilast

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ABSTRACT

Prime objective of this research work is to develop sustain release microsphere of Apremilast by using different polymer ratio to control the drug release from microspheres and to reduce frequent dosing by enhancing patient compliance. Apremilast microspheres were developed by solvent evaporation method by using different polymers like Eudragit RL 100, Ethyl Cellulose and HPMC E5. Optimized Apremilast microspheres was characterized for FT-IR, DSC, particle size, micromeritic properties, entrapment efficiency, % yield, drug content, In-vitro drug release, kinetics release study and Scanning electron microscopy. At last Microspheres are converted into tablet by direct compression method by using suitable excipients and evaluate it. Apremilast Microspheres was formulated by solvent evaporation method using Eudragit RL as polymer in 1:10 Drug: polymer ratio, 10ml dichloromethane, 1% PVA at 1500 RPM stirring speed for 90 mins shows result as (91.50 %) % Yield, (88.72 %) Drug content and (81.52 %) % CDR, this result is best result amongst all other formulation. SEM monographs confirm that microspheres were smooth and spherical shape. Optimized batch F-5 was further taken for compressing a tablet which shows better result than conventional aprezo 30mg tablet. In-Vitro drug release study of Apremilast microspheres loaded tablet show 74.17% CDR in 12 hours compare to slow while aprezo 30mg tablet shows 75.38% CDR in 1 hours followed by 90.45 in 12 hours. Apremilast microspheres loaded tablet shows sustain drug release over a prolonged period of time compare to the marketed tablet which decreases frequent dosing of Apremilast and beneficial in Psoriasis and Psoriatic arthritis.

Keywords: Apremilast, Microsphere, Solvent evaporation method, Tablet, Psoriasis and Psoriatic arthritis.

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INTRODUCTION

New drug delivery system (NDDS) helps to ensure that pharmaceuticals are distributed at a rate that is appropriate for the body's needs during treatment while also reaching the active component to the site of action quickly. Drug delivery systems' (DDS) ability to precisely monitor drug release rates to target specific body regions has a major impact on health care system. Carrier technology offers an intelligent approach by binding the drug to carrier particles such as microspheres, nanoparticles & lipids to drug delivery [1, 2].

An ideal NDDS using carrier technology is most suitable by the coupling of drug to the carrier particles such as the nanoparticles, liposomes, microspheres, microcapsules etc. which modulates the release and absorption characteristics of the drug [3].

Various marketed conventional product gives fast drug release in body, so large dosing frequency is required for that kind of products. Conventional drug delivery is extensively beneficial in many ways and it simply obtained in market place but they have several drawbacks like limited targeting, low aqueous solubility, fluctuation in plasma level and small therapeutic index etc. To overcome those kinds of difficulties, an advanced multiparticulates system has been designed. [4] These systems have valuable in an effective absorption and improved solubility, bioavailability of drugs due to a large surface to volume ratio, a much closer contact with mucus layer and precise targeting of drugs to absorption site. If it is given through oral route than these multiparticulates goes in stomach and then adhere to the mucous linings as stomach empties. Release of drug from this system can be controlled with half-life emptying of stomach and it shows prolonged drug release at extended period of time [4].

Inflammation is a part of both psoriasis and psoriatic arthritis but slight less than a third persons who have psoriasis will get psoriatic arthritis. Psoriasis is a most common chronic inflammatory skin disease which differs in severity form lowest size of scaly red patches to full body parts covering. Psoriatic arthritis is also a skin illness of autoimmune system in which patches of abnormal skin is seen. Apremilast is a novel medicine approved by US food and drug administration which prevent the effect of phosphodiesterase-4 enzymes and accelerate c-AMP level. Also, low level of phosphodiesterase-4 enzyme inhibits various types of inflammatory cytokines such as tumor necrosis factor-alpha and interleukin-23 which have been

responsible for various psoriatic conditions. Conventional product of Apremilast shows an immediate drug release and so it needs frequent dosing which leads to patient intolerance and although cost of product was converted into high. So, overcome of these drawbacks and decrease frequency of dosing this novel and safer Apremilast microsphere is developed. Microsphere of Apremilast undoubtedly improves the solubility as well as increase the stability of drug and enhanced pharmacological action of drug by improving drug release profile. This microsphere releases a drug slowly in sustain manner for prolonged period of time which beneficial in treatment of psoriasis and psoriatic arthritis [5, 6].

MATERIALS AND METHODOLOGY

Materials

Apremilast was obtained Lewens Labs Pvt. Ltd. Dahej. Eudragit RL100 and PVA was from Chemdyes Corporation, Rajkot. Ethyl cellulose was from Fine Chem Industries, Mumbai. Dichloromethane was from ACS Chemicals, Ahmedabad.

Preparation of Apremilast microsphere

Apremilast microspheres are developed by using emulsification (o/w) solvent evaporation method. Drug was taken in combination with ethyl cellulose, Eudragit RL100 and HPMC E5 as polymers. First polymer was dissolved in dichloromethane and drug was added in above solution and mixed systematically. Above organic phase was added drop by drop to PVA solution under magnetic stirrer at high speed on room temperature and stirring is continued until total evaporation of dichloromethane. After evaporation remaining solution was filtered and product was dried. By using above method different batches of microsphere were prepared by taking different polymers to different ratio with drug [7].

Solubility Study

Drug with supplementary amount was dissolved in beaker containing suitable solvent and this supernatant solution was filtered using filter paper. Sample was collected and analyzed in UV spectroscopically. Above process was performed by using various solvents [5].

Calibration Curve of Apremilast

Calibration curve of drug was made by transferring 2, 4, 6, 8, 10 and 12 ml from standard stock solution of 100µg/ml in each 10ml volumetric flask. Volume was adjusted with methanol up to 10ml in volumetric flask. Solution obtained has concentration of 2, 4, 6, 8, 10 and 12µg/ml respectively. Absorbance of the solution was measured at 200 to 400nm wavelength. Calibration curve was prepared by plotting absorbance versus concentration of the drug and regression equation was obtained [5].

Identification of drug by FTIR Spectroscopy and DSC

Potassium bromide IR disc was equipped using drug on hydraulic pellet press which was examine 4000-400 cm^{-1} range in FTIR and found IR Spectrum was related with a reference spectrum of drug. Drug was checked by differential scanning calorimetry for further identification and purification.

Characterization of microsphere

% Yield

It is calculated as the weight of microspheres obtained from each batch divided by total weight of drug and polymer used to prepare that batch multiplied by 100 [9].

% Encapsulation Efficiency

Weighed amount of microsphere are taken and crushed. Then dissolved in buffer solution with the help of stirrer and filtered. The filtrate is assayed by UV spectrophotometer at particular wavelength by using calibration curve [10].

Drug Entrapment efficiency = total amount of drug in microspheres/ total quantity of drug added in preparation × 100

Micromeritic properties

Angle of repose

The fixed funnel method was used for estimating the angle of repose for different formulations.

$\theta = \tan^{-1}(h/r)$

Where, θ is angle of repose, r is the radius, and h is the height [11].

Bulk Density

It is defined as the mass of a powder to the bulk volume. The bulk density of a powder or granules can be depending on particle size distribution, shape of the particles and the adhesion between the particles of powder and granules [12].

Bulk Density = Weight of the Powder /Volume of Powder or granules.

Tapped density

It is a measure used to define void space of powder got after tapping bulk quantity of powder in a measuring cylinder [12]. Tapped Density = Powder weight /Tapped Volume.

Carr's Index or Percentage Compressibility

Compressibility is indirectly related to relative flow rate, cohesiveness and particle size distribution of powder. Tapped density and bulk density of powder material was used to measure compressibility of a powder material. Carr's Index (%) = (Tapped Density – Bulk Density / Tapped density) x 100 [13].

Hausners ratio

It is the ratio of bulk volume to tapped volume or tapped density to bulk density. It is a measure of compressibility of powder. Tapped density and bulk density of powder

material were used to measure Hausners Ratio [14]. Hausners ratio = Tapped density / Bulk density

% Drug Content

It is determined by the method of assay by taking microspheres. Then, weigh suitable number of microspheres take into a volumetric flask and dilute it up to 100ml followed by filtration. Now take the sample for analysis by analytical method. If a smaller number of tablets are available than which should be not be less than 5, may be observed. The content of active ingredient must be applying as per limits i.e., in-between 90% to 110%. Drug content = Concentration of the drug in (mcg/ml) × volume of medium × dilution factor [15].

In-vitro release study

5ml aliquots of dissolution media were withdrawn each time at suitable time intervals (1, 2, 3, 4, 5, 6, 9, & 12 hours.) and replaced with fresh medium. After withdrawing, samples were filtered and analysed after appropriate dilution by using Double beam UV spectrophotometer. The concentration was calculated using standard calibration curve [15].

Scanning electron microscopy (SEM)

Scanning electron microscopy (SEM) was performed to characterize the surface and size of formed microspheres. Microspheres were mounted directly onto the sample stub and coated with gold film under reduced pressure. This film acts as a conducting medium on which a stream of electron was allowed to flow and then photograph was taken with Scanning Electron Microscope (HITACHI S-3400N) [15].

RESULTS AND DISCUSSION

Organoleptic Properties of drug

Physical appearance was determined visually and it was found to be white, amorphous, odourless powder.

Melting Point of Apremilast

Melting point of Apremilast was checked by melting point apparatus. Drug Apremilast filled in one end close capillary. This capillary and thermometer were tied in melting point apparatus. Temperature range was checked at which Apremilast was finally melted. Melting point of Apremilast drug was found to be 154 °C ± 2°C.

Solubility Study of Apremilast

Solubility study was conducted by taking excess amount of drug and dissolve in respective solvents and it found that drug is insoluble in water but freely soluble in methanol, ethanol and PEG 200.

Determination of Wavelength max of Apremilast

Wavelength of Apremilast was found to be 229.74 nm on UV spectrophotometer.

Calibration curve of Apremilast

Standard stock solution was prepared by dissolving drug equivalent to 10 mg dissolved in methanol and volume was made up to 10 ml with same solvent in a volumetric flask. From stock solution 0.2, 0.4, 0.6, 0.8, 1 and 1.2 ml were pipette out and volume was made up to 10 ml with methanol to produce concentration of 2, 4, 6, 8, 10 and 60 µg/ml respectively. Solution was scanned in UV regions 400nm to 200 nm then absorption was measured at maximum λmax. Calibration curve was plotted by using absorbance and concentrations which seen figure 1.

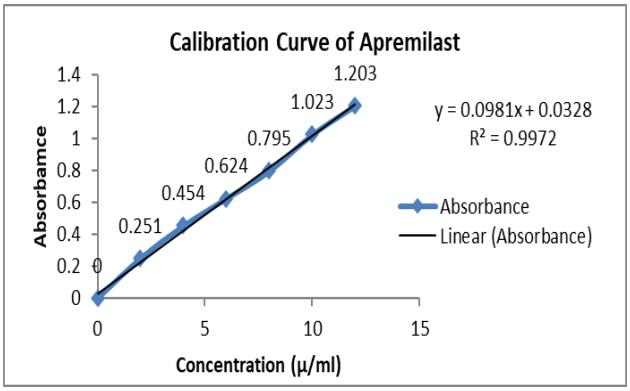

Figure 1: Calibration curve of Apremilast

SEM study of Apremilast microspheres

In figure 2 of scanning electron microscopy found that Apremilast loaded microspheres had rigid in nature, had spherical shape and it was swollen which shows that dug is loaded in microsphere.

Formulation and evaluation of Apremilast microspheres

Table 1: Composition of microspheres

Ingredients	F1	F2	F3	F4	F5	F6
APM: Ethyl cellulose	1:5	1:10	1:15	-	-	-
APM: Eudragit RL 100	-	-	-	1:5	**1:10**	1:15
Dichloromethane (ml)	10	10	10	10	**10**	10
Poly vinyl alcohol (mg)	100	100	100	100	**100**	100
Stirring Speed (RPM)	1500	1500	1500	1500	**1500**	1500
Stirring Time (Mins)	90	90	90	90	**90**	90
Distilled Water (ml)	100	100	100	100	**100**	100

Table 2: Evaluation of Apremilast microspheres

Parameters (Mean ± S.D.) (n = 3)	Apremilast microspheres (Mean ± S.D.) (n = 3)					
	F1	F2	F3	F4	F5	F6
% Yield	84.21±1.4	85.31±1.5	83.24±1.6	90.12±1.5	**91.40±0.8**	89.52±1.1
Encapsulation efficiency (%)	88.36±1.2	89.79±1.6	88.08±1.1	89.29±1.6	**92.72 ± 1.1**	91.22±1.5
Drug Content(%)	79.62±0.8	82.22±0.4	81.23±0.7	84.20±0.4	**88.72±0.4**	87.20±0.4
Particle Size (µm)	460±4	385±5	314±8	284±6	**227.78±4**	264±8
% CDR in 30 Min	74.52±1.5	78.59±1.5	74.27±1.5	78.31±1.5	**81.52 ±1.5**	79.24±1.5

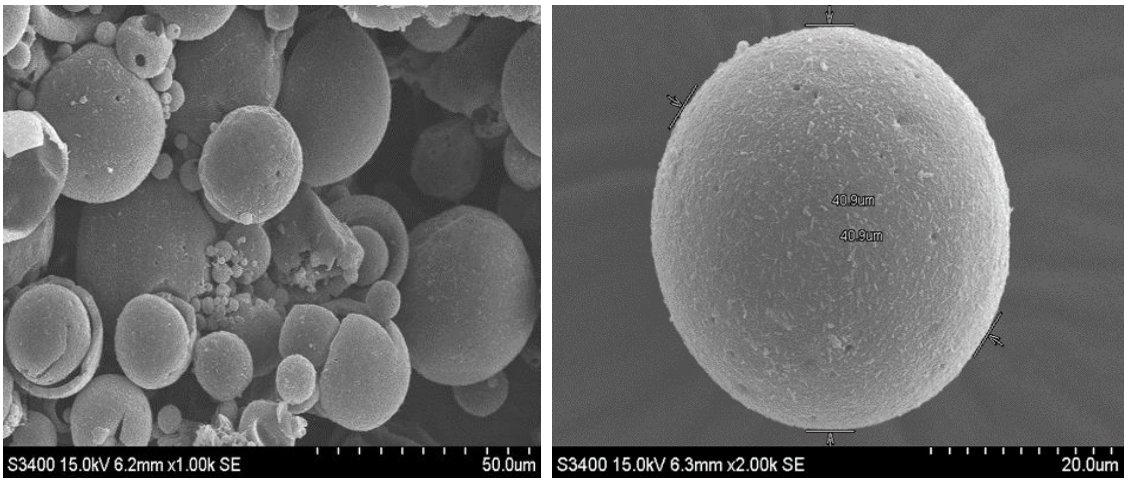

Figure 2: SEM of Apremilast microsphere

Particle size analysis

Figure 3 shows the particle size of microsphere in among all batches F-6 batch shows a less particle size (227.78±2 µm) as compare to all other batches which was display in Table no. 2.

Dose calculation of Apremilast microspheres loaded tablet

300 mg marketed Tablet of Apremilast (Aprezo) contains 30mg of Apremilast as drug.

- ✓ 88.72 mg Apremilast drug is present in 100 mg of Apremilast Microsphere
- ✓ So, 30 mg required Apremilast contain (?) Apremilast Microsphere

30 * 100 / 88.72= **33.81 mg** Apremilast Microspheres

Here 33.81mg of Apremilast Microspheres Required to formulate Apremilast microspheres loaded tablet.

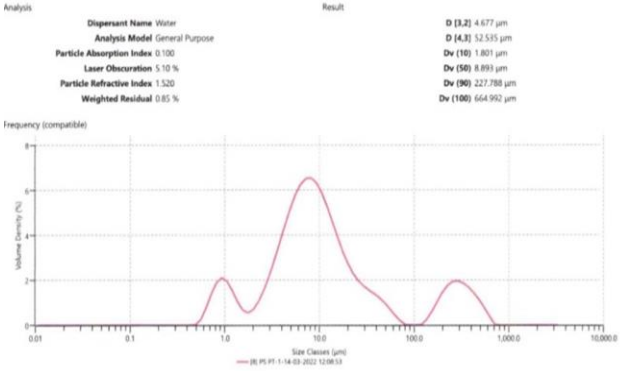

Figure 3: Particle Size of Apremilast microsphere

Table 3: Formulation of Apremilast microspheres loaded tablet

Sr. No.	Ingredients	Quantity
1	Apremilast Microspheres	33.81 mg
2	Mannitol	165 mg
3	HPMC	93.19 mg
4	Talc	3 mg
5	Magnesium Stearate	5 mg

Table 4: Evaluation of Apremilast microspheres loaded tablet

Parameters	Optimized Apremilast microspheres loaded tablet (Mean ± S.D.) (n = 3)	Conventional Aprezo tablet (Mean ± S.D.) (n = 3)
Hardness (kg/cm^2)	3.5±0.2	3±0.2
Weight Variation	Pass	Pass
Friability (%)	0.20±0.04	0.28±0.05
Drug Content (%)	92.23±0.7	90.72±0.8
% CDR (12hrs)	74.17±0.8	90.45±1.2

CONCLUSION

Apremilast Microspheres was formulated by solvent evaporation method using Eudragit RL 100 as polymer in 1:10 Drug: polymer ratio, 10ml dichloromethane, 1% PVA at 1500 RPM stirring speed for 90 mins shows result as (91.50 %) % Yield, (88.72 %) Drug content and (81.52 %) % CDR, this result is best result amongst all other formulation. SEM monographs confirm that microspheres were smooth and spherical shape. Optimized batch F-5 was further formulated into Apremilast loaded tablet shows better result than conventional aprezo 30mg tablet. In-Vitro drug release study of Apremilast microspheres loaded tablet show 74.17% CDR in 12 hours compare to slow where aprezo 30mg tablet shows 75.38% CDR in 1 hours followed by 90.45 in 12 hours. Thus, Apremilast microspheres loaded tablet was successful in maintaining sustain drug release over prolonged period of time and reduce frequent dosing which is useful in treatment of Psoriasis and Psoriatic Arthritis.

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REFERENCES

1. Walia S, Dua J, Prasad N. A Novel Drug Delivery of Microspheres. Journal of Drug Delivery & Therapeutics. 2021; 11(6): 257-264.
2. Choudhary K, Yarraguntla S. Mucoadhesive microsphere for controlled drug delivery. Biological and Pharmaceutical Bulletin. 2004; 1717-1724.
3. Patil N, Thorat S, Upadhyay S. Microspheres: A Novel Drug Delivery System. American Journal of Pharmatech Research. 2020; 10(02): 86-301.
4. Kumar B, Chandiran S, Bhavya B, Sindhuri M. Microparticulate Drug Delivery System: A Review. Indian Journal of Pharmaceutical Science & Research. 2011; 1(1): 19-37.
5. Khadse S, Chalikwar S, Firke S, Baviskar H, Umale A. A Concise Review Based on Analytical Method Development and Validation of Apremilast in Bulk and Marketed Dosage Form. Journal of Drug Delivery & Therapeutics. 2020; 10(2-s): 175-182.
6. Rajpali D, Gupta V. Floating Microspheres Based Nizatidine Gastro Retentive Formulation to Control Release of Drug. Applied Nano Bioscience. 2020; 9(3): 1409-1419.
7. Kataria S, Middha A, Sandhu P, Ajay Bilandi A, Kapoor B. Microsphere A Review. International Journal of Research in Pharmacy and Chemistry. 2011; 1: 1184-1198.
8. Savjani K, Gajjar A, Savjani J. Drug Solubility: Importance and Enhancement Techniques. ISRN Pharmaceutics. 2012; 1-10.
9. Thanoo B, Sunny M and Jaya Krishnan A. Cross-linked chitosan microspheres: preparation and evaluation as a matrix for the controlled release of pharmaceuticals. J Pharm Pharmacol. 1992; 44(4): 283-6.
10. Trivedi P, Verma L, Garud N. Preparation and Characterization of Aceclofenac Microspheres. Asian Journal of pharmaceutics, 2008; 2(2). 110-115.
11. Anandea N, Jain S, Jain N. Conjugated mucoadhesive microspheres for colonic delivery of diloxanide furoate. International Journal of Pharmaceutics. 2008; 182–189.
12. Dhurke R, Jinukula B, Shah S. Formulation and Evaluation of Floating Microspheres Using Factorial Design. International Journal of Recent Scientific Research. 2019; 10(12-B): 36363-36370.
13. Mothilal M, Nagalakshmi M, Swati P, Damodaran N, Manimaran V, Lakshmi K.S. Optimization and Characterization of Chitosan Microspheres of Aceclofenac. IJPSR. 2012; 3(2): 305-315.
14. Nandgude T, Hasabe S. Formulation and Development Modified Release Apremilast Pellets. Asian Journal of Pharmaceutics. 2018; 12(4): S1228.
15. Patel K, Patel M. Preparation and evaluation of chitosan microspheres containing nicorandil. International Journal of Pharmaceutical Investigation. 2014; 4(1): 32-37.
16. Kumar S, Chopra S, Singh S, Kaur J, and Bhatia A. A Comprehensive Review on Tablet Processing and Evaluation. JETIR. 2018; 5(12): 719-732.

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