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FORMULATION, OPTIMIZATION AND EVALUATION OF MESALAMINE TIMED RELEASE DOSAGE FORM

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ABSTRACT

Mesalamine, a medication commonly used to treat inflammatory bowel illnesses, poses difficulties in oral administration due to its pH-dependent release profile and restricted absorption in the gastrointestinal tract. Pelletization is a viable strategy to addressing these concerns because it allows for controlled release and increased bioavailability. Mesalamine pellets were manufactured via extrusion-spheronization and tested for a variety of physicochemical qualities. Different formulations were created using varying amounts of mesalamine, microcrystalline cellulose, and hydroxypropyl methylcellulose. The pellets were evaluated for micrometric characteristics and in vitro drug release profiles under simulated gastrointestinal circumstances. The effect of formulation characteristics on drug release kinetics was investigated using mathematical models. This mesalamine pellets, which were rigorously tuned using a 3^2-factorial design, were assessed for various responses, including drug release. The improved formulation demonstrated drug release over 8 hours, resulting in a delayed therapeutic impact when compared to immediate-release formulations. Finally, the manufactured mesalamine pellets revealed promising properties for delayed release, which could improve patient compliance and therapeutic outcomes in the treatment of inflammatory bowel illnesses.

KEYWORDS: Mesalamine, Pellets, Extrusion-Spherization, Inflammatory Bowel Disease.

INTRODUCTION

In recent years, there has been a significant deal of interest in the development and usage of solid dosage forms that can be ingested and then slowly release the medicine throughout the gastrointestinal tract for around 24 hours. Such dosage is referred to by numerous terms,

including delayed release, extended release, sustained release, and prolonged release.[1] They are commonly referred to as controlled-release preparations.

A modified release preparation may also be classified as a single- or multiple-unit dose form.[2] In the first scenario, the drug dose is combined into a single release unit, whereas in the second, it is divided into a huge number of little release units. A multiple unit dose form is frequently thought to provide a more consistent pharmacological activity.

Enteric coating is a specific type of mechanism that controls release by eroding or dissolving the coating.[3] An enteric coating is resistant to disintegration in acidic circumstances but freely soluble in the more basic conditions of the intestinal system.[4] Enteric coating can be used to protect acid-labile medications or to prevent stomach distress caused by high doses of certain pharmaceuticals.[5]

Mesalamine is used to treat ulcerative colitis, a disorder that produces swelling and ulcers on the lining of the colon, large intestine, and rectum, as well as to keep ulcerative colitis symptoms under control.[6] mesalamine is an anti-inflammatory substance. It works by preventing the body from manufacturing a certain chemical that might cause inflammation.[7]

The FDA has approved it for the induction and maintenance of remission in ulcerative colitis patients.[8] Mesalamine is increasingly being used to treat a variety of colonic illnesses, including IBD (inflammatory bowel disease), Crohn's disease, and ulcerative colitis.[9] The colon is a site where drugs can be delivered locally or systemically. Many attempts have been made in the last decade for producing the appropriate formulation to release the mesalamine exactly in the colon without being released in other areas of the gastrointestinal tract (GIT), to avoid premature absorption and loss of medicine.

1.1 Pellets

Pellets are agglomerated powders or granules made up of bulk medicines and excipients. They are made up of small, free-flowing spherical or semispherical solid units that typically range in size from 0.5-2mm. These are often used for oral administration. The generic words "granulation" and "pelletization" are sometimes used interchangeably, and the units produced are referred to as granules, pellets, agglomerates, or spheroids with no obvious differentiation between them.[10]

Pelletization is a highly promising approach for multiparticulate drug delivery systems. The interest in pellets as dosage forms filled into hard gelatin capsules or compressed into disintegrating tablets has been constantly increasing, because their multiparticulate nature offers many important pharmacological and technological advantages over conventional single-unit solid dosage forms.[11]

Advantage of Pellets

Pellets increase flow characteristics during formulation development.

- Capsules flow freely and pack easily, resulting in consistent and reproducible fill weights.
- Pellets are less prone to dosage dumping.
- It decreases medication buildup, which is especially beneficial for irritating drugs.[12]

Disadvantage of pellets

- Capsule filling can increase expenses, while tab letting can ruin pellet film coatings.
- Pellets typically range in size from 1 to 2mm, depending on formulation.[13]

Pelletization Technique

It is one of the most popular methods for preparing pellets since it produces a large number of pellets while avoiding the disadvantages of other dosage forms. Produces pellets with a high active ingredient loading capacity without producing much larger particles, as well as particles with a consistent size distribution and excellent flow characteristics.[14]

1. Dry Mixing and Granulation.
2. Extrusion.
3. Spheronization.
4. Drying.
5. Screening.[15]

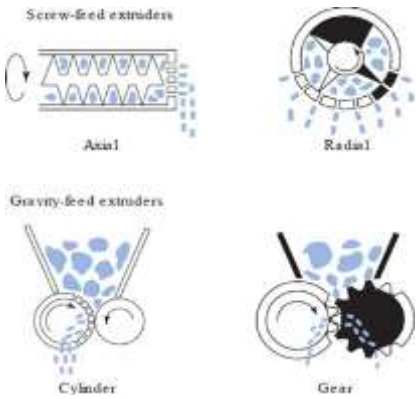

Fig no. 01: Types of Extruder.

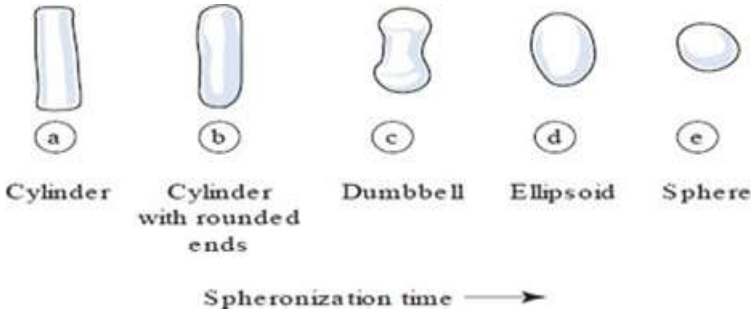

Fig no. 02: Shape transitions during a spheronization process.

2. MATERIALS AND METHOD

Materials

Mesalamine medication was obtained as a gift sample from Pellucid Pharma, Gujarat, India, and ethylcellulose from Paxal Chemistry, Karnataka, India. Microcrystalline cellulose, cellulose acetate phthalate, and hydroxypropyl methyl were purchased from Pharmafabrikon in Madurai, Tamil Nadu, India.

Methodology: preformulations of active pharmaceutical ingredients

Preformulation investigations

Pre-formulation testing is the initial stage in developing logical dosage forms for a medicinal ingredient. Pre-formulation studies are the process of improving drug delivery by determining the physicochemical qualities of excipients that may affect drug performance and the development of an effective, stable, and safe dosage form. It establishes a framework for combining drugs with pharmaceutical excipients in dosage form.[16]

Solubility

The saturated solubility of Mesalamine API in water and different pH 4.5, 6.0, 6.5,6.8,0.1N HCL was performed and reports are given in result section.

Determination of bulk and tapped density[17]

A amount of 20g of powder from each formula was put into a measuring cylinder. The tapping was repeated until no additional volume change was detected. The bulk density and tapped density were computed using the calculations below.

Bulk density = mass of powder / bulk. Volume of powder

Tapped density = mass of powder/tapped volume of the powder

Determination of Carr's Index

It aids in determining the force needed to break the friction between the particles and the hopper. Carr's Index is reported in percentage and calculated as (ρtapped-ρbulk)/ρtapped*100.

Hausner's ratio

Hausner's ratio is an indirect measure of how easily powder flows. Hausner's ratio was determined as the ratio of tapped density to bulk density.

Hausner ratio=tapped density/bulk density

Analytical Method: Standard Plot curve for Mesalamine[18]

Prepare 0.1N HCL (diluent)

In a 1000ml volumetric flask, add several 100ml of water, then 8.3 ml of 37% hcl, then fill the volumetric flask up to 1000ml with water.

Standard Stock Solution Preparation

Weighed accurately about 10 mg of mesalamine and transferred it to a 100 ml volumetric flask with 35 ml of diluent. Sonnicated the content in a volumetric flask and added diluent to make a volume of 100ml. Pipette 2ml, 4ml, 6ml, 8ml, and 10ml of this solution into a 10ml volumetric flask, then dilute the volume with diluent.

Compatibility studies[19]

To prepare a sample, combine the medicine and excipient with a spatula before filling a vial with a rubber lid.

Differential Scanning for Drug Excipients Calorimetry

The compatibility of drugs and polymers under experimental settings is a key precondition for formulation. It is therefore vital to establish that the medicine does not react with the polymers and excipients under experimental settings, does not impair the product's shelf life, and has no other undesirable effects on the formulation. The thermal properties of mesalamine were investigated using a Shimadzu Differential Scanning Calorimeter 60 from Japan. Samples were collected at a scanning rate of 10°C/min across a temperature range of 0-300°C in an inert environment flushed with nitrogen at a rate of 20ml/min.

METHODOLOGY

- Extrusion spheronization is the most advanced method of pelletization. Pellet formulation procedures include dry mixing, extrusion, and spheronization.
- Mesalamine, microcrystalline cellulose, and povidone K30 were well mixed in a container.
- Hydroxypropyl methyl cellulose and ethyl cellulose were measured and passed through a 44 mesh screen before being combined with the drug-containing physical combination.
- The mixture was then passed through sieve 60.
- Cellulose acetate phthalate, talc, and magnesium stearate were processed through sieve 60 individually.
- In the container, combine this mixture with the preceding one and add enough water to achieve wet granulation.
- This was put to the extruder, and the extrudate was collected and added to the spheronizer. Spherules were then collected from the outlet.

Extrusion

It was the second stage of spheronization after granulation. This procedure required driving the wet mixture through the extruder's dies to generate long cylindrical rods of uniform diameter.

Sphereonization process

It entailed depositing the extruded cylinders onto the spheronizer's rotating plate, known as the friction plate, where the extrudate was broken up into smaller cylinders of similar length to their diameter. Frictional forces caused these plastic cylinders to become rounded.

Drying

To get the necessary moisture content in the finished pellet, drying was performed. The pellets could be dried at room temperature in a standard oven.

Coating procedure: enteric coating

Prepare the enteric coating solution

The enteric coating of the pellets was achieved by producing a 1.5% solution of cellulose acetate phthalate in acetone and stirring for 30 minutes to obtain a transparent solution.

Procedure for Enteric Coating

Dispense and weigh the initial total weight of pellets, and the enteric coating solution was poured onto the traditional pan coater pellets. The pellets were dried for 15 minutes at 35-45°C.[20]

Table 1: Formulation chart of Mesalamine pellets.

S.no	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Mesalamine(mg)	249.6	249.6	249.6	249.6	249.6	249.6	249.6	249.6	249.6
2.	Microcrystalline cellulose (mg)	202.2	170.4	182.4	170.4	140.4	152.4	140.4	110.4	122.4
3.	Povidone(mg)	42	42	42	42	42	42	42	42	42
4.	Cellulose acetate phthalate(mg)	30	30	30	30	30	30	30	30	30
5.	Talc(mg)	3	3	3	3	3	3	3	3	3
6.	Magnesium stearate(mg)	3	3	3	3	3	3	3	3	3
7.	Hydroxy propyl methyl Cellulose :Ethyl cellulose (mg)	72 (1:1)	102 (1:1)	90 (1:1)	102 (1:2)	132 (1:2)	120 (1:2)	132 (1:4)	162 (1:4)	150 (1:4)
8.	Total	600	600	600	600	600	600	600	600	600

Methodology: Design of Experiments (DOE)

The formulation of the pellets was optimized using full factorial 3^2 design, which is preferable for response surface methods when optimizing complicated formulations. The studies were developed with three parameters and two responses. Design-Expert® 11 (Stat-Ease Inc., Minneapolis, MN, USA) was utilized for experimental design and statistical analysis. The experimental design and statistical analysis were carried out with Design-Expert 11 (Stat-Ease Inc.). In all studies, the percentages of X1, X2, and X3 were combined. %. The percentage medication release (Y1) and porosity (Y2) were employed as answers to optimize the pellet composition. The nine designed trials were fitted with quadratic and polynomial models. Various statistical parameters obtained by ANOVAs were compared to select the best fitting model for each response.

Table 2: Three full factorial 32 design.

Run	Factor1 A:HPMC:EC	Factor 2 B:MCC
1	20	25.4
2	12	25.4
3	20	18.4
4	27	18.4
5	12	33.7

6	27	25.4
7	12	18.4
8	27	33.7
9	20	33.7

Table 3: List of Independent variables.

S.No	Name	Units	Low(-1)	Intermediate (0)	High(+1)
1.	MCC	%	18.4	25.4	33.7
2.	HPMC:EC	%	012	20	27

Table 4: List of dependent variables.

Response	Name	Units
Y1	Drug release	%
Y2	porosity	%

Characterization and Evaluation of Prepared Pellets[21]

Bulk density

A weighed quantity of 2 gm pellets was put into a 10 ml measuring cylinder without tapping, and the volume occupied by the pellets was measured.

Bulk density = mass of powder / bulk. Volume of powder

Tapped density

Weighed quantities of 2 mg pellets were placed in a graduated cylinder, and the volume occupied by granules was recorded.

Tapped density = mass of powder/tapped volume of the powder

Carr's Compressibility Index

Pellets' compressibility refers to their ability to decrease in volume under pressure. The percentage compressibility of pellets was calculated using both untapped and tapped density, and the result is known as Carr's compressibility index.

Carr's Index equals (ρtapped-ρbulk)/ρtapped*100.

Hausner's Ratio

It measures the drug's frictional resistance. It was determined by the ratio of tapped density and bulk density.

Friability[22]

A total of 10 g pellets were weighed and placed in the friabilator chamber. It rotated at a speed of 25 rpm. After 100 spins (4 minutes), the pellets were removed from the friabilator, and the intact pellets were weighed collectively.

Porosity

Pellets' bulk and tapped density were homogeneous in terms of particle size distribution. The actual density defines the porosity of the pellets and is determined using a liquid displacement method.[23]

Drug content by Assay

1. Prepare a standard stock solution (0.1N HCL solution)

50 mg of mesalamine standard was carefully weighed and placed to a 100ml clean dry volumetric flask. 50 ml of diluent was then added and sonicated to dissolve the drug. The solution was diluted, mixed, and passed through a 0.45µm membrane filter.

2. Preparation of Standard Solution

4ml of the above-mentioned standard stock solution was transferred to a 10 ml clean, dry volumetric flask, and the volume was adjusted with diluent.

3. Preparation of test solution

20 grams of carefully weighed capsulated pellets were pulverized. 120mg of powdered pellets were correctly weighed, corresponding to 50 mg of mesalamine in a 100ml volumetric flask. To this, 50ml of diluent was added. and sonicated for thirty minutes. The solution was allowed to cool. To test absorbance at 330nm, 4ml of the solution was removed, diluted with 10ml, and filtered through a 0.45µm membrane filter.[24]

***Invitro* drug release**

Apparatus: usp apparatus -2 (paddle)

Acid stage: 0.1 N HCL

RPM: 100

Medium: 900 ml of 0.1N HCL

Temperature: 37 ± 0.5 °C

Sampling interval: 1 hour

UV absorbance: 330nm.

Preparation of 0.1N HCL

59.5 ml of concentrated HCL was precisely weighed and placed into seven liters of water.

Procedure

The procedure involved adding six capsulated pellets to six distinct dissolution flasks, each with 900ml of pH 1.2 dissolution liquid (0.1 N HCl). The test was conducted in a USP dissolving device at 37 ± 0.5 °C in medium and 100 rpm.

Apparatus: USP apparatus -2 (paddle)

Buffer stage: 6.8 phosphate buffer

RPM: 100

Medium: 900 ml of 6.8 phosphate buffer

Temperature: 37 ± 0.5 °C

Sampling interval: 1 hour

UV absorbance: 330nm.

Preparation of 6.8 buffer

To make 6.8 buffer, weigh 6.8g of monobasic and 0.89 gram of sodium pellets and dissolve them in 1000 ml of water. Adjust the pH to 6.8.

Procedure

Six capsulated pellets were placed in six dissolution flasks, each with 900 cc of dissolution liquid. (pH 6.8 phosphate buffer). The test was carried out in a USP dissolving apparatus at 37 ± 0.5°C in medium and 100 rpm.

Drug Release Kinetics[25]

Data from the dosage form were analyzed using Zero order, First order, Higuchi, and Peppas models to determine the mechanism and rate of release. The best-fit model was chosen based on its R and n values.

Evaluation of capsules[26]

Disintegration test: The disintegration time of the prepared capsules was measured using a disintegration instrument. Six capsules were put in six tubes of the basket rack assembly, which was operated using distilled water at 37±2°C. The capsules were monitored, and the time it took for each capsule to completely disintegrate was recorded.

Moisture content test

Use gravimetric analysis to assess the moisture content of the capsule. The container used was a sealed glass that had been dried until the weight remained consistent. One gram of capsules was placed in the container and placed in an oven at 100 degrees Celsius. The container and gelatine were chilled using a desiccator. This method was repeated until the weight was consistent.

Capsule weight variations

Individual weights of 20 capsules were obtained, and the average weight was computed using the following formula.

$$\text{Weight Variation} = \frac{\text{(Capsule weight minus Average weight)}}{\text{The average weight of capsules}} \times 100$$

Lock length

To determine lock length, ten capsules from each formulation trial batch were filled and manually measured with vernier callipers. The average of ten capsules was recorded.

Stability studies

The optimized formulation (F10) was subjected to accelerated stability tests. A suitable quantity of pellets were stored in glass containers at 40°C/75% RH for one month. Samples were taken at 15-day and one-month intervals and tested for porosity and dissolution. Samples were graded based on their description (color).

RESULTS AND DISCUSSIONS

Solubility

The components used in pellet formulation were chosen for their highest mesalamine solubility. The solubility of mesalamine in various vehicles was investigated, and the findings were given. Mesalamine solubility was substantially higher in 6.8 phosphate buffer than in 6.5 phosphate buffer. As a result, 6.8 phosphate buffer was more soluble than the other vehicles.

Table no. 5: Solubility Study of Mesalamine API.

S.No	pH	mg/ml
1.	Water	0.68
2.	4.5 acetate buffer	1.25
3.	0.1N HCL	1.65
4.	6 phosphate buffer	2.22
5.	6.4 phosphate buffer	4.32
6.	6.5 phosphate buffer	5.94
7.	6.8 phosphate buffer	8.47

Micromeritic properties of mesalamine API

The bulk density of a powder was calculated by measuring the volume of a known mass of powder sample that passed through a sieve and into a graduated cylinder. The results showed that the powder mixes of the formulation have good flow characteristics. The tapped density was the increased bulk density obtained by mechanically tapping a container containing the powder sample. The results showed that the formulation's powder mixes have good, tapping flow. Carr's Index was calculated for powder compressibility using tap density and bulk density.

Table no. 06: Micromeritic properties of mesalamine API.

S.No	Properties	Results
1.	Bulk density	0.237 g/ml
2.	Tapped density	0.507 g/ml
3.	Compressiability index	54.659%
4.	Hausner ratio	2.157

Standard Plot curve for Mesalamine

The calibration curve was plotted with 0.1 N HCL as the solvent. In a 100-volumetric flask, weigh 10 mg of the medication and dilute with 0.1 N HCL. From this reserve solution, 2ml, 4ml, 6ml, 8ml, and 10ml were extracted and diluted to 10ml. The solution was made at concentrations of 20, 40, 60, 80, and 100 µg/ml, and the absorbance was measured at 330nm against a blank using a UV spectrophotometer. The pure substance was discovered using a UV spectrum ranging from 200 to 400 nm. The maximal wavelength of mesalamine was determined to be 330nm, with a regression coefficient of R2 =0.9949. Thus, mesalamine follows Beers Lambert's law.

Table no. 07: Standard Plot Curve of Pure Drug.

S.No	Concentration(mg/ml)	Absorbance
1.	20	0.296
2.	40	0.492
3.	60	0.692
4.	80	0.882
5.	100	1.095

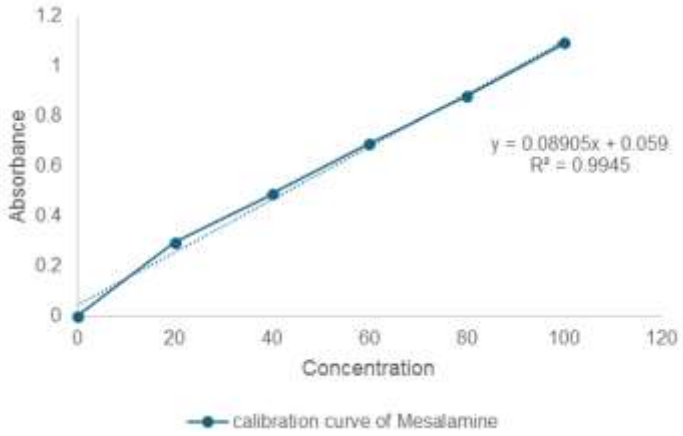

Fig. No. 03: Standard Plot Curve of Pure Drug.

Differential scanning calorimetry

DSC (differential scanning colorimetry) is often used to detect drug-excipient interactions and thermal stability of drugs or drug-excipient mixtures. The interactions result in the shifting or absence of the characteristic melting endotherm. The DSC analysis of the pure medication mesalamine and mesalamine with excipient (HPMC, MCC, EC) were used for comparison. These are utilized in pellet formulations. Thermogram of mesalamine (pure drug) exhibited a sharp endothermic peak at 287.19°C indicating the melting point of the drug. Thermogram of mesalamine with excipients exhibited a peak at 283.26, the endothermic peak intensity of mesalamine was slightly reduced and shifted to a lower temperature (from 287.19 to 283.26 ℃). Minor shifting with diminished intensity may be due to solid-solid interaction rather than incompatibility.

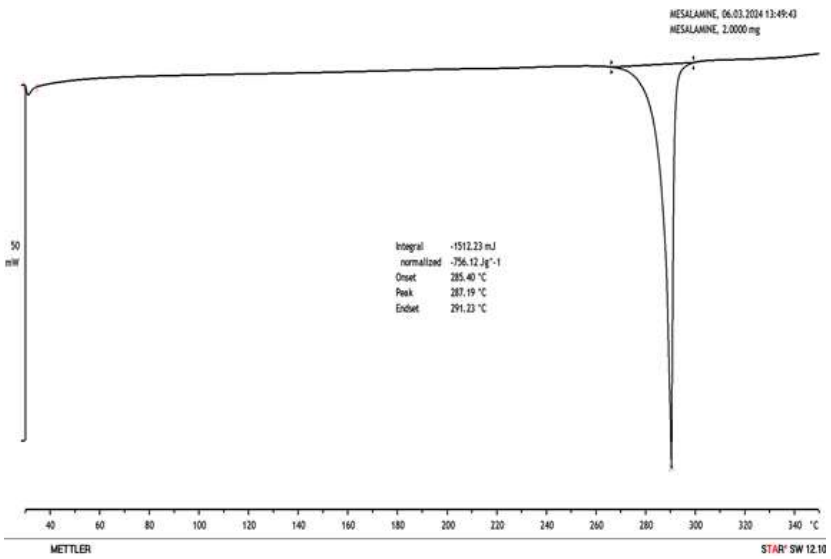

Fig. 03: DSC of mesalamine Api.

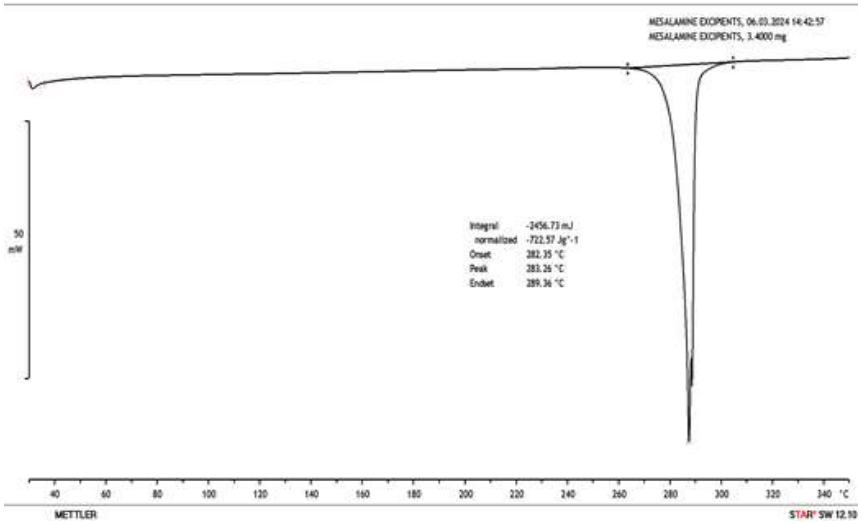

Fig. 04: DSC of mesalamine Api with excipients.

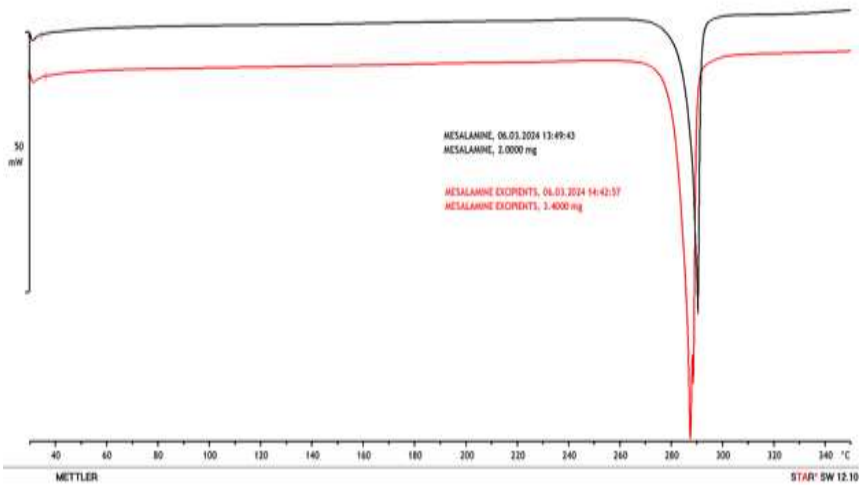

Fig. 05: Overlay of DSC.

Micromeritic properties of prepared mesalamine pellets

Bulk density is an important characteristic for pellet formation. Bulk density measurements ranged from 0.53 to 0.64 grams per milliliter. The values were low in formulations containing a large proportion of HPMC and ethyl cellulose. The results showed that the powder blends of formulation have good flow pellet qualities. Tapped density of pellets is defined by the mass-to-volume ratio of powder. The tapped density for mesalamine formulations ranged from 0.60 to 0.90g/ml. The Carr's index of the formulation of mesalamine pellet was determined to be between 20.17% and 36%, indicating that the pellet was satisfactory. The hausner ratio was utilized to give appropriate ability flow of pellets, which was determined by tapped density and bulk density of pellets.

Table 8: Micromeritic properties of prepared mesalamine pellets.

Formulation	Bulk density(gm/ml)	Tapped density(gm/ml)	Hausner ratio	Carr's index(%)
F1	0.57	0.66	0.82	20.17%
F2	0.55	0.69	0.80	19.117%
F3	0.57	0.67	0.86	13.63%
F4	0.54	0.68	0.7	22.5%
F5	0.64	0.8	0.56	20%
F6	0.60	0.83	0.72	27.71%
F7	0.62	0.61	0.75	25%
F8	0.53	0.60	0.54	10%
F9	0.54	0.63	0.60	15.62%

Friability

Table no. 09: Friability.

Formulation	Friability(%)
F1	0.34
F2	0.54
F3	0.58
F4	0.79
F5	0.65
F6	0.47
F7	0.54
F8	0.2
F9	0.24

Pellet friability was tested in the same equipment under different conditions. The friability of pellets was determined by initial weight and final weight of samples. All the samples exhibited similar residue moisture content. The percent of friability was obtained from

formulation F1-F9. Formulation F8 shows better friability (0.2%) it shows better friability than other formulations.

Drug content by assay

Table 10: Assay.

Formulations	Assay(%)
F1	98.45
F2	98.43
F3	97.67
F4	101.1
F5	97.48
F6	98.05
F7	102.06
F8	99.58
F9	96.14

***Invitro* drug release**

Table 11: Cumulative drug release(%) all formulations(F1-F9).

Time(hours)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	7.20%	7.64%	8.54%	7.34%	8.99%	9.90%	7.98%	6.18%	8.79%
2	15.25%	13.66%	15.48%	14.27%	15.9%	19.09%	14.94%	15.66%	17.42%
3	31.07%	32.17%	30.39%	31.22%	33.3%	29.90%	34.46%	34.59%	31.62%
4	40.28%	43.49%	39.36%	41.23%	46.28%	36.8%	47.7%	47.39%	45.67%
5	52.17%	49.32%	45.67%	53.03%	65.28%	48.60%	55.2%	54.28%	59.72%
6	60.38%	60.55%	56.35%	62.4%	70.51%	59.92%	69.32%	63.6%	69.63%
7	66.70%	64.18%	63.31%	68.25%	76.28%	64.28%	77.20%	72.26%	75.23%
8	70.58%	75.18%	71.15%	72.84%	81.4%	72.76%	82.53%	86.3%	83.06%

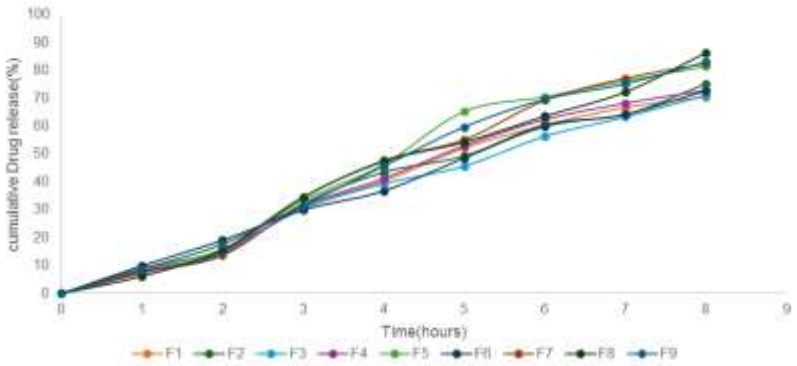

Fig. 6: Cumulative drug release (%) all formulations (F1-F9).

In vitro drug release study of mesalamine pellets was carried out in two dissolution mediums, 2 hours in 0.1 N HCL and 6 hours in phosphate buffer. The cumulative% drug release of (up to 70% in all formulations).

OPTIMIZATION

Table 12: 3^2 Full factorial design.

Run	Factor1 A:HPMC:EC	Factor 2 B:MCC	Response 1 *Invitro* drug release(%)	Response 2 Porosity(%)
1	20	25.4	81.4	24
2	12	25.4	72.84	33
3	20	18.4	75.18	50
4	27	18.4	71.15	30
5	12	33.7	82.53	25
6	27	25.4	72.76	20
7	12	18.4	70.5	55
8	27	33.7	83.06	27
9	20	33.7	86.3	29

The formulation of the pellets was optimized using full factorial 3^2 design, which is preferable for response surface methods when optimizing complicated formulations. The studies were developed with three parameters and two responses. Design-Expert® 11 (Stat-Ease Inc., Minneapolis, MN, USA) was utilized for experimental design and statistical analysis.

Optimization

ANOVA for Quadratic model

Table 13: Summary of ANOVA for response parameters of Y1 (*Invitro* drug release).

Source	Sum of squares	df	Mean square	f- value	P-value	
Model	277.32	5	55.46	16.50	0.0216	Significant
A-HPMC:EC	0.2017	1	0.2017	0.0600	0.8223	
B-MCC	204.87	1	204.87	60.95	0.0044	
AB	0.0036	1	0.0036	0.0011	0.9759	
A^2	60.21	1	60.21	17.91	0.0241	
B^2	12.04	1	12.04	3.58	0.1548	

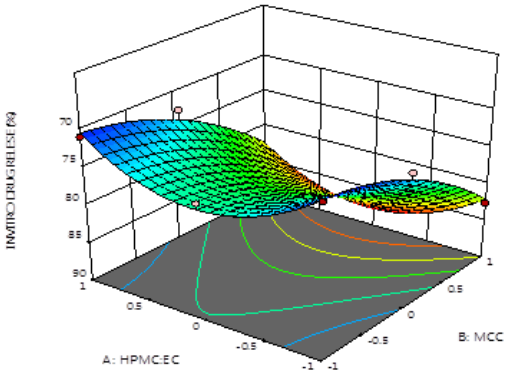

Fig. no. 7: Response surface methodology for *Invitro* drug release, where A is HPMC:EC, Where B is MCC.

Response 2: Porosity

ANOVA for Quadratic model

Table 14: Summary of ANOVA for response parameters of Y2 (Porosity).

Source	Sum of squares	df	Mean square	F- value	P-value	
Model	1112.03	5	222.41	19.51	0.0170	Significant
A-HPMC:EC	216.00	1	216.00	18.95	0.0224	
B-MCC	486.00	1	486.00	42.64	0.0073	
AB	182.25	1	182.25	15.99	0.0280	
A^2	14.22	1	14.22	1.25	0.3454	
B^2	213.56	1	213.56	18.74	0.0227	

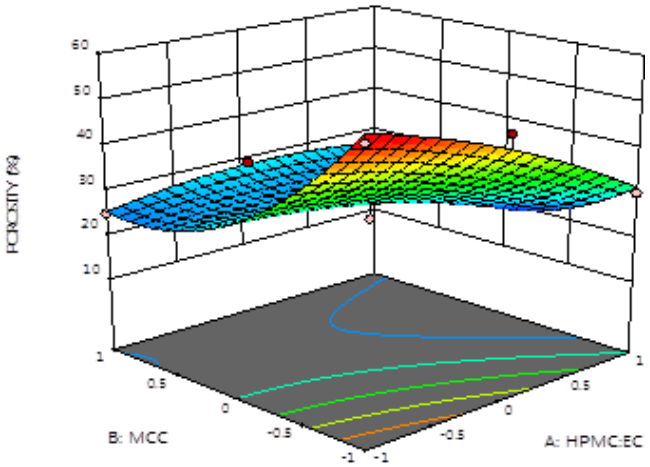

Fig. no. 8: Response surface methodology for porosity, where A is HPMC:EC, Where B is MCC Optimized formulation (mesalamine pellets, F10).

Table 15: Optimized formulation.

S.NO	HPMC:EC	MCC	*invitro* drug release	porosity
1	0.014	1	88%	28.7%

Table 16: Point prediction.

Solution 1 of 100 Response	Predicted Mean	Predicted Median	Obs	Std Dev	SE Mean	95% CI low for Mean	95% CI high for Mean	95% TI low for 99% Pop	95% TI high for 99% Pop
invitro drug release	72.2009	72.2009	**88%**	1.83	1.2021	68.375	76.026	55.582	55.582
porosity	42.964	42.964	**28.7%**	3.3	2.213	35.91	50.009	12.3607	73.5673

Optimized F10 Formulation

Table 17: *Invitro* study of mesalamine in 0.1N HCL and pH 6.8 buffer.

Time (hours)	Absorbance (nm)	Amount of Drug release (mg)	Cumulative drug release (%) and mean±SD, *n*=3
0	0	0	0
1	0.069	14.20	5.22±0.33
2	0.146	25.20	13.58±0.51
3	0.343	88.25	36.50±0.44
4	0.470	120.21	49.40±0.57
5	0.566	145.43	56.29±0.76
6	0.640	165.35	67.42±0.62
7	0.760	185.25	78.23±0.70
8	0.856	221.27	88±0.34

Table 18: Comparative dissolution profile of optimized formulation with marketed product.

Time (hours)	Marketed formulation (%)	Optimized formulation (%)
0	0	0
1	7.23	5.22
2	18.45	13.58
3	30.05	36.5
4	39.88	49.4
5	48.90	56.29
6	60.01	67.42
7	69.20	78.23
8	76.80	88

F2 : Similarity Factor	77
F1 : Dissimilarity Factor	9

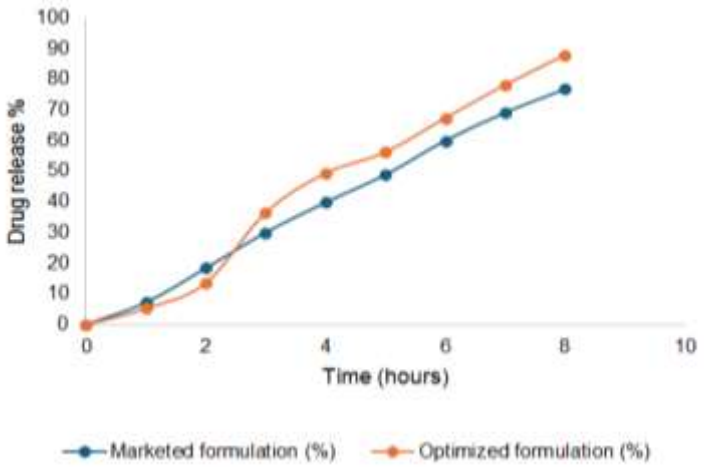

Fig no. 09: Comparative dissolution profile of optimized formulation with marketed product.

Cumulative percentage drug release of optimized formulation F10- 88% in comparison with market product where the drug release 76.80%

Discussions of optimization

The 3^2 full factorial was design was applied to optimize the mesalamine pellets. The results of responses were fitted to Design-Expert 11 software and statistical analysis suggested different fitting models and their relationship to the variables. The drug release (Y1), % porosity (Y2) were important variables in the preparation of pellets that maintained a stable formulation and improved the oral absorption of insoluble drugs. Pellets can enhance the bioavailability of poorly water-soluble drugs by increasing the surface area available for dissolution. By considering polynomial linear regression analysis, the Y1 equation is given as below in the **Equation No. 1**

$$\textbf{Drug release} = +52.12+0.17XA+4.34XB-0.02XAB-4.19XA^2+1.42XB^2 \ldots\ldots\ldots\ldots\ldots (1)$$

The influence of the main and interactive effects of the independent variables on the particle size was studied using polynomial equation, and it was found to be statistically significant ($P< 0.0001$), as determined using ANOVA.

Porosity influences the rate and extent of drug release from pellets. porosity typically leads to faster drug release. By characterizing porosity, control the drug release kinetics to achieve desired drug release. The influence of the main and interactive effects of the independent variables on the porosity was studied using polynomial **Equation No.2,** and it was found to be statistically significant ($P< 0.0001$), as determined using ANOVA

$$\textbf{Porosity} = +23.4-5XA-8XB+5.2XAB-2.12XA^2+9.2XB^2 \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (2)$$

Optimized pellets of mesalamine were evaluated for *invitro* drug release and porosity. According to point prediction the mean predicted was 72.20% and observed value was found to be **88%** for *invitro* drug release. Also mean predicted value was 42.9% and observed was found to be **28.7%** for porosity. And F10 Formulation was found to have correlating results with the observed value of *invitro* drug release. Therefore, optimization solution for formulation F10 was HPMC:EC (0.014%) and MCC (1%), and invitro drug release (88%) and porosity(28.7%)

Kinetics models

Table 19: Kinetics Models.

Kinetics models	R^2 value	K value & n value
Zero order kinetics	R^2=0.9777	K=28.49
First order kinetics	R^2=0.7776	K=0.1045
Higuchi model	$R^{2=}$0.9833	K=45.09
Kors-peppas model	R^2=0.9849	n=0.8954

- The optimized formulation follows zero order kinetics because it fits the equation and R^2 was found to be nearer to 1 suggesting delayed release, this formulation does not follow first order kinetics as the R^2 was not nearer to 1. Follows Higuchi model suggesting the release occurs by diffusion and R^2 value was found to be closer to 1.
- This optimized formulation follows korsmeyer-peppas model as the n value is. 0.8954.suggesting non-fickian mechanism of drug release and R^2 value was found to be closer to 1.

Evaluation of capsules

Table 20: Evaluation of Mesalamine Timed-Release Capsule.

Formulation	Disintegration time (minutes)	Moisture content test(%)	Capsule weight variation(%)	Lock length(mm)
F10	4.02±2.09	13.38±0.69	9.5±0.1	23.5±0.43

Mesalamine Timed-Release Capsule

Disintegration test

The results obtained was 4.02±2.09 min, which has meet the requirements of less than 5minutes.

Moisture content

The moisture test was carried out to evaluate the drying of hard-shell capsule low water levels cause capsule shells to be brittle and break easily. the moisture content of hard shell produced was 13.38%, which shows this optimized formulation fulfill the requirements.

Capsule weight variation

The uniformity of dosage units may be demonstrated by determining weight variation. Weight variation of prepared capsules was within the limit (±7%).

Lock length: Average of ten capsules was noted the obtained value for the optimized formulation was about lock length value 23.5mm.

Optimized formulation

Fig. 9: Optimized Formulation.

The optimized formulation was filled in size 0 capsule and evaluated for release properties and stability study.

Stability studies of mesalamine pellets is given below.

Parameter	Initial	15 days	1 month
description	Pale brown	No difference	No difference
Average weight(mg)	599	598.5	597.30
Assay(%)	99.65	99.61	99.59
Invitro drug release(%)	88	87.5	87.1
Porosity(%)	28.7	28.6	28.3

The optimized formulation was subjected to stability studies for a period of 1 month to assess their stability. Samples were loaded into humidity chambers at controlled humidity and temperature(40°C/75%RH). The samples were evaluated based on their porosity and drug dissolution, average weight, description. The physical appearance of the pellet was found to be same after period of 1 month, average weight of each pellet was found to be 598.5 mg in 15 days and 597.30 mg after period of 1 month. The porosity of pellet was found to be 28.3% after a month and % drug release of the formulation after period of one month was found to be 87.1%.

CONCLUSION

Mesalamine with low solubility and low permeability under BCS class 4 possess some problems in conventional form. Formulation of mesalamine delayed release capsule have gained a great deal of importance for improving drugs with low solubility and low permeability. In addition, the optimized formulation showed a higher dissolution rate and low percentage porosity, which improved oral bioavailability of the drug. Extrusion-

spheronization was found to be an efficient pelletization method for achieving sphericity and strength. Additionally, this fast and efficient technique offers high drug loading capacity. Short term accelerated stability shows, optimized formulation was stable with porosity and dissolution parameter which provided better patient compliance.

REFERENCE

1. Matschke C, Isele U, van Hoogevest P, Fahr A. Sustained-release injectables formed in situ and their potential use for veterinary products. Journal of Controlled Release, Dec. 13, 2002; 85(1-3): 1-5.
2. Varum FJ, Merchant HA, Basit AW. Oral modified-release formulations in motion: the relationship between gastrointestinal transit and drug absorption. International Journal of Pharmaceutics, Aug. 16, 2010; 395(1-2): 26-36.
3. Mahato RI, Narang AS. Pharmaceutical Dosage Forms and Drug Delivery: Revised and Expanded. CRC Press, 2017 Nov 22.
4. Maderuelo C, Lanao JM, Zarzuelo A. Enteric coating of oral solid dosage forms as a tool to improve drug bioavailability. European Journal of Pharmaceutical Sciences, Oct. 1, 2019; 138: 105019.
5. Diwakar Manohar P. (Formulation and Evaluation of Lansoprazole Enteric Coated Pellets (Doctoral dissertation, JKK Nattraja College of Pharmacy, Komarapalayam).
6. Singh J, Sharma M, Singh H, Arora P, Utreja P, Kumar S. Formulation, Characterization and In Vitro Evaluation of Mesalamine and Bifidobacterium bifidum Loaded Hydrogel Beads in Capsule System for Colon Targeted Delivery. AAPS PharmSciTech., Mar. 2024; 25(3): 1-30.
7. Actis GC, Pazienza P, Rosina F. Mesalamine for inflammatory bowel disease: recent reappraisals. Inflammation & Allergy-Drug Targets (Formerly Current Drug Targets-Inflammation & Allergy)(Discontinued), Mar. 1, 2008; 7(1): 1-5.
8. Sands BE, Sandborn WJ, Panaccione R, O'Brien CD, Zhang H, Johanns J, Adedokun OJ, Li K, Peyrin-Biroulet L, Van Assche G, Danese S. Ustekinumab as induction and maintenance therapy for ulcerative colitis. New England Journal of Medicine, Sep. 26, 2019; 381(13): 1201-14.
9. Travis S. Advances in therapeutic approaches to ulcerative colitis and Crohn's disease. Current Gastroenterology Reports, Nov. 2005; 7(6): 475-84.
10. Sharma M, Joshi B, Bansal M, Goswami M. Formulation and evaluation of colon targeted tablets of mesalazine. Journal of Drug Delivery and Therapeutics, Sep. 15, 2012; 2(5).

11. Nanjibhai CV. Formulation and Evaluation of Floating Drug Delivery System Containing Theophylline as a Model Drug(Doctoral dissertation, Rajiv Gandhi University of Health Sciences (India)).
12. Liu P, Ju T, Qiu Y. Diffusion-controlled drug delivery systems. Design of controlled release drug delivery systems, 2006; 107-37.
13. Sanopoulou M, Papadokostaki KG. Controlled drug release systems: Mechanisms and kinetics. Biomed. Membr.(Bio) Artif. Organs, Nov. 29, 2017; 2: 1-33.
14. Nakao SI. Determination of pore size and pore size distribution: 3. Filtration membranes. Journal of Membrane Science, Nov. 28, 1994; 96(1-2): 131-65.
15. Siepmann J, Siegel RA, Siepmann F. Diffusion controlled drug delivery systems. InFundamentals and applications of controlled release drug delivery, Sep 27, 2011; 127-152). Boston, MA: Springer US.
16. Kalia YN, Guy RH. Modeling transdermal drug release. Advanced drug delivery reviews, Jun 11, 2001; 48(2-3): 159-7.
17. Patel H, Panchal DR, Patel U, Brahmbhatt T, Suthar M. Matrix type drug delivery system: A review. J Pharm Sci Biosci Res., Nov. 2011; 1(3): 143-51.
18. Kanjickal DG, Lopina ST. Modeling of drug release from polymeric delivery systems—a review. Critical Reviews™ in Therapeutic Drug Carrier Systems, 2004; 21(5).
19. Aguzzi C, Cerezo P, Salcedo I, Sánchez R, Viseras C. Mathematical models describing drug release from biopolymeric delivery systems. Materials Technology, Sep. 1, 2010; 25(3-4): 205-11.
20. Hari P. Formulation and Evaluation of Gastro Retentive Methyl Cellulose-Sodium Alginate Microspheres for Controlled Release of Curcumin (Doctoral dissertation, College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore).
21. Chang RK, Robinson JR. Sustained drug release from tablets and particles through coating. Pharmaceutical Dosage Forms, Jul. 27, 1990; 3: 199-302.
22. Bermejo M, Sanchez-Dengra B, Gonzalez-Alvarez M, Gonzalez-Alvarez I. Oral controlled release dosage forms: dissolution versus diffusion. Expert Opinion on Drug Delivery, Jun. 2, 2020; 17(6): 791-803.
23. Wang S, Liu R, Fu Y, Kao WJ. Release mechanisms and applications of drug delivery systems for extended-release. Expert Opinion on Drug Delivery, Sep. 1, 2020; 17(9): 1289-304.

24. Khan N, Craig DQ. The influence of drug incorporation on the structure and release properties of solid dispersions in lipid matrices. Journal of controlled release, Dec. 12, 2003; 93(3): 355-68.
25. Wang J, Dlamini DS, Mishra AK, Pendergast MT, Wong MC, Mamba BB, Freger V, Verliefde AR, Hoek EM. A critical review of transport through osmotic membranes. Journal of membrane science, Mar. 15, 2014; 454: 516-37.
26. Li B, Guinness SM, Hoagland S, Fichtner M, Kim H, Li S, Maguire RJ, McWilliams JC, Mustakis J, Raggon J, Campos D. Continuous production of anhydrous tert-butyl hydroperoxide in nonane using membrane pervaporation and its application in flow oxidation of a γ-butyrolactam. Organic Process Research & Development, May 23, 2018; 22(6): 707-20.