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Research Article

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" FORMULATION AND EVALUATION OF MOUTH DISSOLVING FILM OF ALOGLIPTIN."

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ABSTRACT:

The aim of this study was to prepare and statistically optimize a pullulan-based sublingual film containing Alogliptin (ALO) mixture, by solvent casting technique to provide a promising remedy for type 2 diabetes. Sublingual films were optimized by employing a central composite design created by the Design Expert® software. The optimized formula was further determined using a novel eco- friendly micellar HPLC method. The separation was carried out on a Kinetex C18 column (100 mm × 4.6 mm i. d, 2.6-µm particle size) with isocratic elution at a flow rate of 1 mL/min and UV detection at 230 nm. The micellar aqueous mobile phase used for the separation was composed of 50 mM sodium dodecyl sulfate, 15% pentanol, and 50 mM sodium dihydrogen phosphate (pH 3.5). The anti-diabetic effects of ALO sublingual films on the blood glucose levels of diabetic rats and their effect on the pancreas and kidney histopathology were studied. The developed method was accurate, and precise and can be used for the simultaneous estimation of both drugs without any interference in their sublingual films. Moreover, the greenness of the suggested method has been evaluated by different tools; analytical Eco-scale and the Green Analytical procedure Index, which shows that it has the least environmental impact.

The ALO sublingual film optimal formula showed mechanical strength of 2.69 ± 0.23 N/mm2, folding endurance of 69 ± 2.13 times, and in-vitro disintegration of 71.7 ± 1.23 s indicating acceptable formulation and mechanical parameters.

A significant improvement in glycemic control where the blood glucose level was normalized (137 ± 23) after 4 h compared to the commercial drugs (247 ± 27.4) at $p < 0.05$ was attained. Additionally, islets of Langerhans appeared apparently normal with average size and intact cells with the improvement of the histopathological examination of renal tissues. This study introduced a successful and promising sublingual film as a drug delivery system of ALO mixture for the treatment of type 2 diabetes.

Introduction

Mouth-Dissolving Film

The pharmaceutical industry is fast becoming interested in drug delivery systems because the drug dissolves or disintegrates within a minute without the application of water or chewing. These systems also increase drug bioavailability due to better clinical profiles through perhaps ameliorating oro-mucosal absorption as compared to conventional oral delivery. Alternately, thin films that rapidly dissolve or break apart in the buccal cavity were introduced in the market not long ago. The new form of medication is mouth-dissolving films, which disintegrate or dissolve in the mouth. These really thin and postage-stamp sized films contain pharmaceutical excipients or active substances. They are also used on any mucous membrane such as the tongue. The films hydrate immediately, stick at the point of application, dissolve or disintegrate upon contact with the saliva, and, thus, the film releases the drug to be absorbed in the mucous membrane. They may also be adjusted to make sure that they do not affect the rapid nature of dissolving, but instead facilitated oral gastric absorption.

These dosage forms are more appropriate to the liquid dosage forms in that they do not require water to administer thus possessing the properties of precise dosage and being unable to choke a patient as the case with tablets and capsules. Consideration of absorption of the medication in the mouth, throat and esophagus as the saliva enters into the stomach, after undergoing the dissolution stage enhanced the efficacy of the medication by way of treatment.

In such case, there is a significant increase in the bioavailability of the drug as compared to conventional form of tablets dosage forms. In the past few years, fast-dissolving buccal film drug delivery systems have gained recognition as a big new drug delivery vehicle. In most cases, they are used on pharmaceutical and nutraceutical products. It is the latest among the drug delivery technology and they provide a highly convenient method of consuming vitamins and prescription medication. Mouth-dissolving films may also be administered in the form of a local anesthetic to toothache, oral ulcers, cold sores, or teothing, when local action in the mouth is required.

To achieve an action that is systemic, it is advisable that the mode of action be oral. About 60 percent of all formulations belong to solid-dosage forms. The most widely used dosage form is the tablet because of the ease of production, shipment, and compliance by the patient. Generally, children, elderly, and prohibited people have a hard time swallowing the conventional tablet. To overcome this problem a new formulation was developed e.g. mouth-dissolving films.

To prepare MDF, hydrophilic polymers are used that disintegrate fast on a tongue or in a buccal cavity to enable the medicine to get into the bloodstream via the buccal lining. In drugs which have a lot of first-pass metabolism.

Special features of mouth-dissolving films

- Mental illness, handicapped, and uncooperative patients are easier to administer.
- There is no use of water.
- It can also be formulated to be good in terms of mouthfeel and also leaving no or very little residue after mouth application.
- The ability to provide the advantages of liquid medication in solid form of preparation.
- Overcomes the unacceptable taste of the drugs.
- Cost effective.

Need to formulate Mouth Dissolving

Film

- This can only be achieved through the adoption of a non-invasive drug administration system; this is because the current drug delivery technologies are not highly accepted by patients and their compliance to this technology is low.
- Mouth dissolving film (MDF) can be used by patients with motion sickness and diarrhea who will not have an easy access to water during their journeys.
- The internal muscles, as well as the control nerve systems, are not integrated, so people cannot eat well.Tremor of hands and Dysphagia have been identified to majorly affect the aged people.
- The mentally challenged and psychiatric patients.

Dysphasia

is common in children and adults. An issue such as dysphasia has been seen in about 35 percent of the general adult population, probably 30-40 percent of the elderly and in 18-20 percent of all individuals in the long-term care facilities as has been estimated in a piece of research. The predominant complaints about the pills are their difficulties in swallowing which are caused by their size, surface, shape and flavour. Dosage forms should be easily swallowed by the old age, juvenile, and traveling patients who may not always get access to of water. The findings make it apparent that a surgical procedure like FDDS as a dose form is urgently required to increase patient compliance because it makes the tablets dissolve in the mouth, and patients do not need to chew them or drink an additional amount of water.

Market view

Poor patient adherence keeps causing necessities of non invasive methods of delivery systems. existing delivery regimes, small sizes of market to the companies and uses of drugs,as well as, exorbitant expenses of dealing with the diseases. Pharmaceutical marketing is one of the reasons as to why the number of fast-dissolving and disintegrating products in the market is going up. When a pharmacological molecule nears the expiry date of its patent, the pharmaceutical companies often develop a new and improved dosage form of the same. The dosage form offers a dose or a method of dose that is more convenient to its patient population, thus making the producer of the dosage form enjoy the added benefit of having a greater market exclusivity. The rapid dissolving and disintegration compositions are similar to some. already available formulations of long release. The fast dissolving or disintegrating dosage form would prolong market exclusivity, enhancing revenue, and at the same time access a significantly under treated and underperserved patient population.

1.4 Advantages of dissolving films on the mouth

i. Flexible dosage.
ii. The use of water is not necessary
iii. No way to choke on it
iv. Anti-flavouring.
v. More steadiness.
vi. Improved patient compliance.
vii. The drug will have a reduced first pass effect in the liver.
viii. Local and local-site activity.

RESULT AND DISCUSSION:

Pre-formulation study of Alogliptin Drug:

The essential component is that a drug must possess chemical and physical definitions prior to formulation of a dosage form.

In the development of a dosage form, pre-formulation studies furnish the data necessary to determine the character of drug ingredient as well as gives a

guideline of drug combination with pharmaceutical excipients.

In this work, pre-formulation studies of the compatibility of the drug were carried out.Organoleptic properties:

The drug sample was observed for color, odor, and texture appearance (see table below).

Test	Specification	Observation
Colour	White to off white crystalline powder	White to off white crystalline powder
Odour	Odourless	Odourless
Taste	Bitter	Bitter
Appearance	Powder	Powder

Melting Point Determination:

The melting point of Alogliptin was determined by the capillary tube method. It wasfound to be 228 to 232 °C, as shown in the table.

Sample Drug	Reported	Observed
Alogliptin	181 to 186°C	185 °C

Solubility analysis

The task of investigating the solubility can be done by making saturated solutions of the drug in a total of four non-volatile solvents, such as PEG 400, water, buffer, ethyl alcohol and methanol.

Solvents	Specification	Observation
Methanol	Completely Soluble	Complies
PEG-400	Soluble	Complies
Buffer	Soluble	Complies

Spectroscopy study of Alogliptin

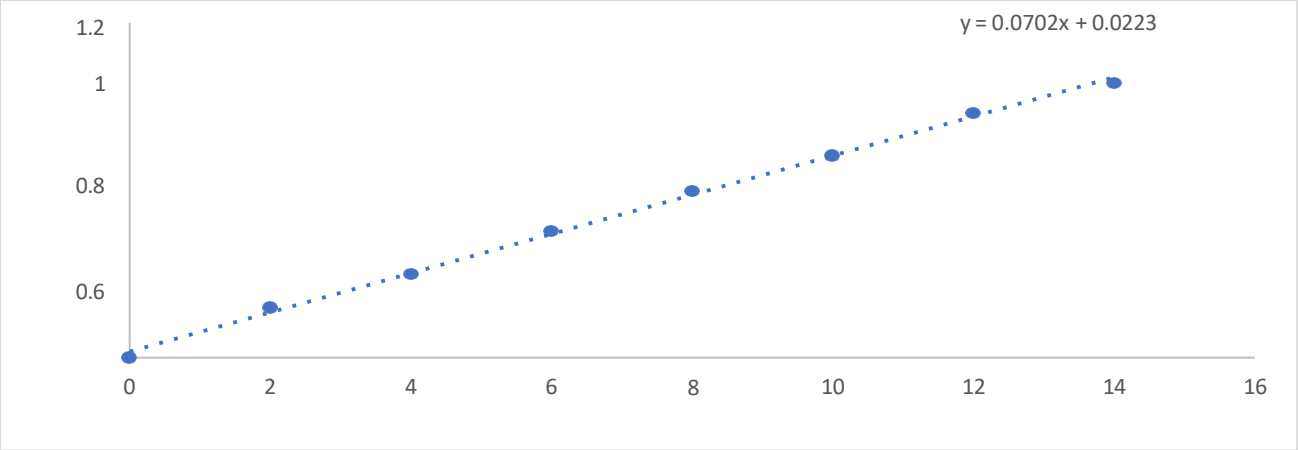
Determining the Alogliptin Calibration Curve Using PH 6.8 phosphate Buffer:

On a twin-beam UV spectrophotometer, the alogliptin solution exhibited the maximum absorbance of wavelength 280 nm after the scan was done with 400 to 200 nm. Its R2 shows a value of 0.9948, which indicates that its standard graph of Alogliptin is a good straight line.

Table 5: Calibration curve of Alogliptin

Concentration (ppm)	Absorbance
0	0
2	0.178
4	0.298
6	0.454

8	0.598
10	0.724
12	0.876
14	0.984



Calibration curve of Alogliptin. FTIR Studies

The mixture of the drug-polymer contained all the characteristic peaks that were present in the Alogliptin, compatibility of the two different substances. Since no significant change in the main peak of the Alogliptin was observed in the drug-polymer physical combinations and was also and chemically compatible, then, the results showed that the functional group was not interfering. The spectrum confirmed that significant changes in chemical integrity of the drug did not happen.

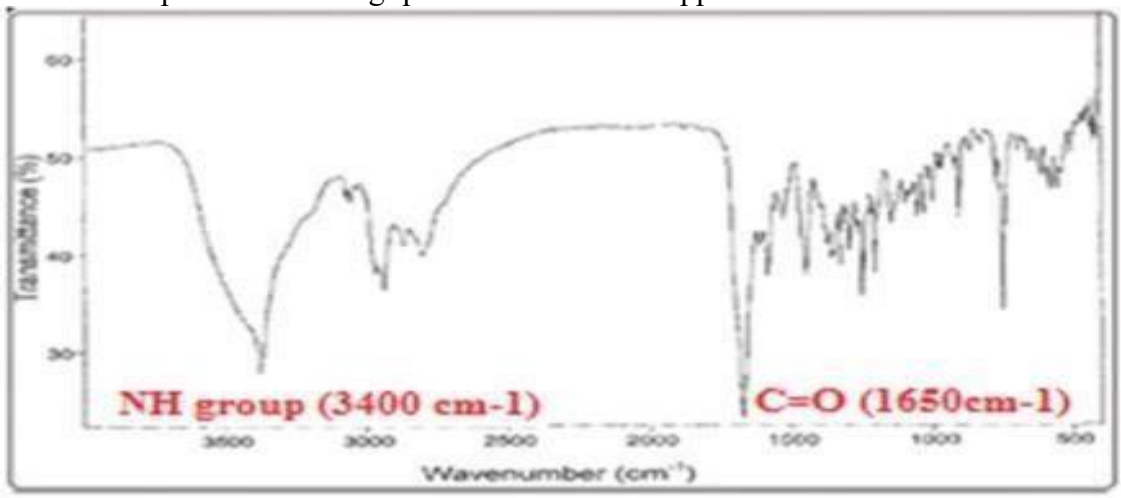


Figure 9: FTIR of Alogliptin.

Interpretation	Pure Drug Values
N-H Stretch	3450.80
C-H Stretch	3050.45
O-H Stretch	3250.78

C=O Stretch	1650.80

Evaluation of Trial Batches of Oral Film:

The average weight, thickness, a total number of folds that an oral film can endure, the surface pH, percentage moisture as well as medication contents are given as trial batch findings. It was found out that all-physical features of the ready oral film were practically within management.

Table 6: Physical Evaluation of Trial Batches of oral film

Batch Code	Average Weight (mg)	Thickness (mm)	Disintegration Time (sec)	Folding Endurance (times)
F1	126.5	0.16	65	240
F2	120.8	0.13	55	298
F3	-	-	-	-
F4	135	0.25	95	230
F5	-	-	-	-
F6	138	0.27	130	170

Table 7: Physical Evaluation of Trial Batches of oral film

Batch Code	Percentage Moisture loss (%)	Surface pH	Drug Content (%)	Dissolution Study
F1	0.60	6.8	80.25	60.30
F2	1.41	6.8	95.45	89.55
F3	-	-	-	-
F4	1.50	6.8	75.14	70.35
F5	-	-	-	-
F6	0.47	6.8	65.25	74.26

Dissolution Study:

The dissolution profile of the soluble film of C is performed on a dissolution device that has a pH 6.8 phosphate buffer as the dissolution medium and 100 rpm. 5 ml of the solution was removed at 2, 4, 6, 8, and It was 10-minutes and the same volume of medium was replaced with fresh medium. Measurement of the percentage of medication release versus a time graph was carried out. The following table presents the observation of films that are oral suitable.

Table 8: In -Vivo Drug Release of Trial Batches

Time (in mins)	Cumulative Drug Release

	F1	F2	F4	F6
0	0	0	0	0
2	23.45	28.95	24.20	23.48
4	28.56	50.56	31.27	32.23
6	38.80	67.70	41.18	38.20
8	55.25	78.68	61.38	67.01
10	67.28	89.35	73.20	74.60

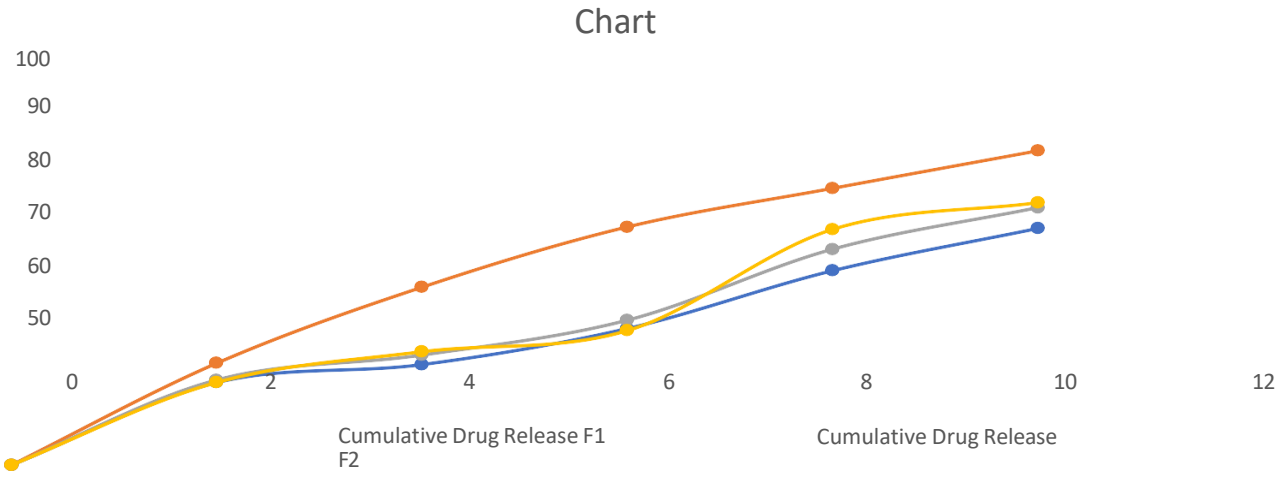


Figure 10: Graph of In- Vitro Dissolution Study of Trial Batches.

Diffusion Study:

In-vitro diffusion study of the prepared oral soluble film was done through the Franz diffusion cell technique. The in vitro characterization of the oral soluble film formulation was done in the Franz diffusion cell.

Table 9: In-Vitro Diffusion study of Oral Film

Time (in mins)	Cumulative Drug Release			
	F1	F2	F5	F4
0	0	0	0	0
2	16.4084018	20.27882348	18.65221718	17.30589199
4	28.35003505	35.97624814	29.05785813	27.78343612
6	52.35590749	54.85747441	47.39888117	49.13152048
8	60.23558546	65.90638856	61.73788758	62.44236035
10	66.10153216	77.80340396	70.59802225	68.78254587

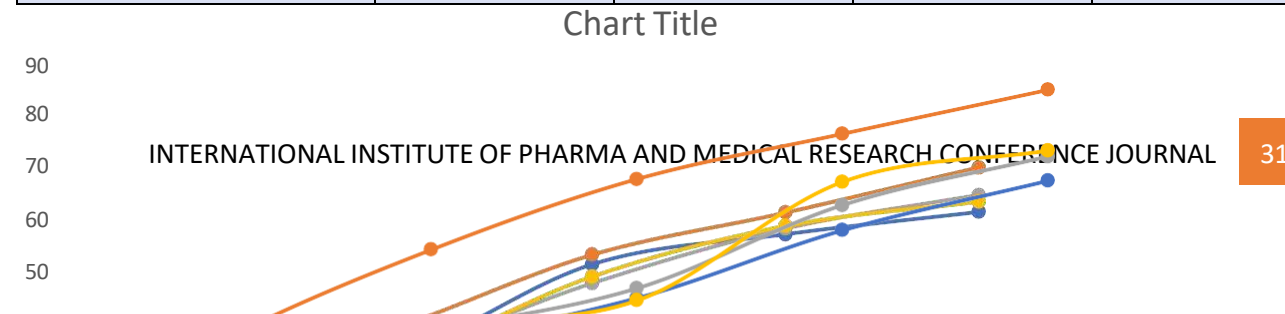


Figure 11: Graph of In-Vitro Diffusion Study of Trail Batches

Evaluation of factorial batches:

Physical Evaluation of Factorial Batches:

The results of factorial batches of the oral film average weight, thickness, folding strength, surface pH, percentage moisture and medication content are given below.

Table 10: Physical Evaluation of Factorial Batches of oral film

Batch Code	Average Weight (mg)	Thickness (mm)	Disintegration Time (sec)	Folding Endurance (times)
F2 1	130.5	0.20	80	140
F2 2	125.7	0.14	57	180
F2 3	135	0.22	85	148
F2 4	140.6	0.25	110	130
F2 5	132.5	0.27	110	138
F2 6	138.6	0.21	75	154
F2 7	150.8	0.25	115	130
F2 8	151.5	0.27	120	138
F2 9	137.9	0.23	80	50
F2 10	124.5	0.16	65	90

Table 11: Physical Evaluation of Factorial Batches of oral film

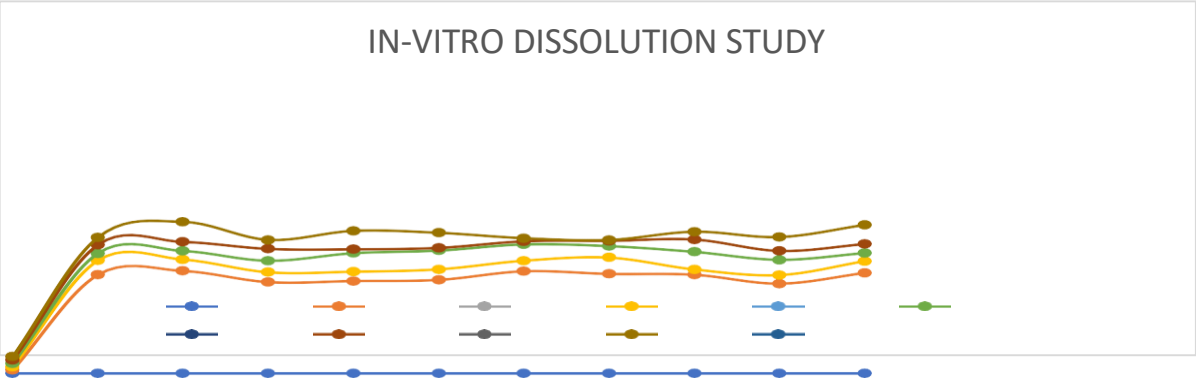
Batch Code	Percentage Moisture loss (%)	Surface pH	Drug Content (%)	Dissolution Study
F2 1	0.60	6.9	94.92	81.58
F2 2	0.40	6.8	94.19	90.93
F2 3	0.70	6.8	93.70	80.10
F2 4	0.48	6.8	93.79	85.56
F2 5	0.50	6.8	95.80	84.38

F2 6	0.62	6.8	95.12	81.11
F2 7	0.48	6.9	94.08	80.06
F2 8	0.55	6.8	95.34	85.04
F2 9	0.80	6.9	94.50	81.81
F2 10	0.45	6.8	93.03	89.14

Dissolution studies:

Table 12: In-Vitro Drug Release of Factorial Batches

Time (in mins)	Cumulative Drug Release (%)									
	F2 1	F2 2	F2 3	F2 4	F2 5	F2 6	F2 7	F2 8	F2 9	F2 10
0	0	0	0	0	0	0	0	0	0	0
2	59.180	61.458	54.758	55.430	56.123	61.295	59.709	59.180	53.850	60.308
4	67.745	68.302	60.658	61.030	62.431	67.638	69.488	62.352	59.008	67.387
6	72.047	73.452	67.587	72.151	73.682	77.418	76.361	72.925	68.167	72.224
8	77.154	78.854	74.704	74.457	75.325	79.268	79.533	80.325	73.475	77.625
10	**81.584**	**90.930**	**80.104**	**85.561**	**84.383**	**81.118**	**80.061**	**85.048**	**81.819**	**89.140**



2: Graph of In- Vitro Dissolution Study of Factorial Batches.

Stability Study

The stability study of the final

optimized batch F2 was performed for 1 month at 40 °C and 75% RH. Initial results and 1-month results were compared and found satisfactory. The batch was found stable during stability. The results were record in the table below.

Parameter	Initial	After 1 Month	After 2 Month
Weight variation (mg)	125.5	121.5	121
Thickness (mm)	0.14	0.13	0.13
Surface pH	6.8	6.8	6.8
Drug content %	94.19	93.20	92.80
Percentage moisture loss	0.40	0.28	0.28
In vitro disintegration time (Sec)	57	59	59
Folding endurance	180	175	173

Conclusion

The aim of the study was to optimize and characterize the mouth-dissolving film of Alogliptin. Formulation, F2, was chosen as the best formulation depending on the outcomes of the evaluation parameters. The F2 2 formulation has yielded positive results in stability analysis. There was not any greater difference between the characteristics at the start and finish of a month. Consequently, F2 2 formulation was done by batch optimization.

Material

materials used in preparation of mouth dissolving film is Alogliptin, HPMC, Polyethylene glycol, Mannitol, citric acid and flavouring agent.

PREPARATION METHOD OF MOUTH DISSOLVING FILMS

There are three options of producing the film and they can be:

1) Solvent casting

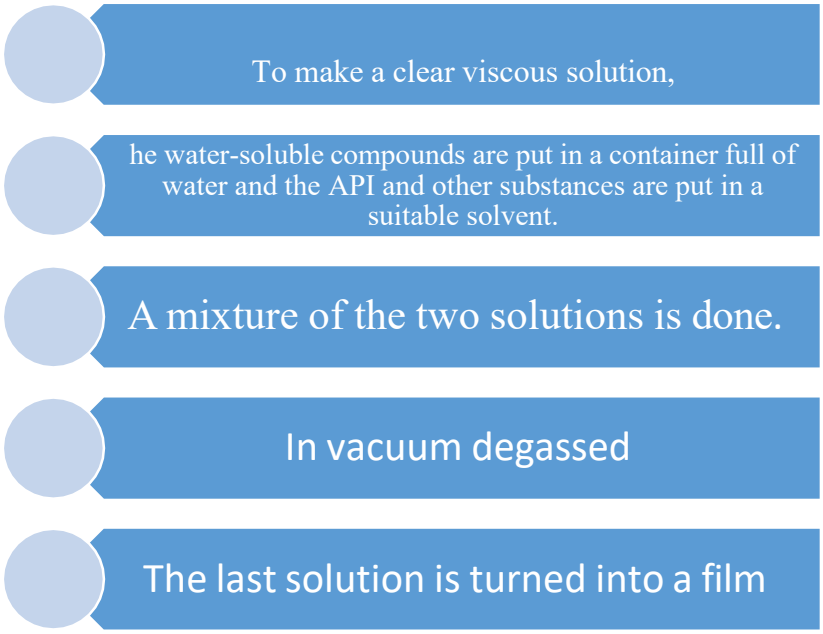
Secondly, the hot melt extrusion

3) Semi-solid casting

4) Compaction of solid dispersion

5) Rolling

1. Solvent Casting Technique.



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