CHAPTER 7

FOEMULATION DESIGN AND METHODOLOGY

FORMULATION DESIGN AND METHODOLOGY FOR THE PREPARATION OF MICROPELLETS

7.1 INTRODUCTION

From the data obtained from preformulation studies (Chapter 5) and from the results of optimization of various process parameters (Chapter 6), the author arrived at a set of values to prepare the final set of formulation of the frusemide loaded calcium alginate micropellets, an oral, non-conventional, microparticulate drug delivery system. The method of preparation was kept in accordance with ionotropic gelation technique[1,2] as discussed earlier in (Chapter 2). The design for the formulations were done as per factorial design[3,4,5] experimentation programs to prepare different batches of micropellets[6] containing Frusemide. The design was made keeping all the parameters constant and only varying the proportions of sodium alginate and Acrycoat E30D (aqueous dispersion of acrylic polymer) dispersion. Several physicochemical properties and the release characteristics of the prepared micropellets were studied. The data generated were statistically analyzed for the development of a suitable mathematical model which can describe the relationship between the release kinetics and the concentrations of polymers. From the statistical data, a conclusion can be drawn about an optimized formulation among all the possible combinations, which can meet the desired objective of controlling the release of drug in the physiological system.

7.2 MATERIALS

1. Frusemide – Aventis Pharma Ltd., Ankleshwar
2. Sodium Alginate --- Loba Chemie, Mumbai
3. Calcium Chloride --- Ranchem, India
4. Acrycoat E30D --- Corel Pharma, Ahmedabad
5. Distilled water – Processed in-house

7.3 OPTIMIZED PARAMETERS

The following process variables were investigated (concentration of sodium alginate; concentration of calcium chloride; curing time; height of dropping; variation of drug loading; stirring speed and stirring time) and the different batches thus produced were analyzed for size, shape, ease of preparation, drug content and drug release. On the basis of the result obtained the process parameters were optimized. Different batches of micropellets were then prepared by using the optimized process variables and the only variation followed in the optimized formulations were the use of different release controlling polymers. Nine set of formulations were prepared using Acrycoat E30D (E1, E2, E4); Acrycoat L30D (L1, L2, L4) and Acrycoat S100 (S1, S2, S4) at concentration levels 1%, 2% and 4% w/w. Nine formulations were subjected to several characterization studies. From the outcome of the studies Acrycoat E30D was optimized for the final set of formulations.

The formulation variables that were optimized during the preformulation study are summarized in the following Table 7.1.

Table: 7.1 – Optimized Parameters of the Process Variables

SL.NO.	PARAMETER	OPTIMIZED LEVEL
1	Concentration of Calcium chloride	5%w/v
2	Drug loading	30%w/w
3	Drying time and mode	6 hrs in hot air oven
4	Drying Temperature	60°C
5	Curing / Hardening time	30 min
6	Stirring time and speed	30 min at 500 rpm
7	Needle size	17G
8	Height of dropping	2cm above the level of $CaCl_2$ solution
9	Syringe	Glass syringe
10	Release controlling polymer	Acrycoat E30D

7.4 THE FORMULATION DESIGN – FULL 3^2 FACTORIAL DESIGN[3]

Micropellets of frusemide were prepared by full 3^2 factorial design. Only **two** variables, with variations at **three** levels, namely, high, medium and low, were observed by varying the concentrations of Sodium alginate and Acrycoat E30D. Hence, 3^2 model designs were selected. High, medium and low levels of sodium alginate were 4%w/v, 2%w/v and 1%w/v respectively and that for Acrycoat E30D the levels were 4%w/w, 2%w/w and 0%w/w. All the other parameters were kept unchanged from its optimized level. The formulation design is tabulated in the Table 7.2.

Table 7.2 Full 3^2 Factorial design for the formulation of frusemide loaded calcium alginate micropellets.

Batch No./ Formulation Code	Sodium alginate	Acrycoat E30D
F1	-	-
F2	-	0
F3	-	+
F4	0	-
F5	0	0
F6	0	+
F7	+	-
F8	+	0
F9	+	+

Level	Sodium alginate (%w/v)	Acrycoat E30D (%w/w)
+	4.0	4.0
0	2.0	2.0
-	1.0	0.0

Constants: Calcium chloride concentration – 5%w/v, Drug loading concentrations- 30%w/w

7.5 Preparations of Frusemide loaded calcium alginate micropellets

Mucilage of sodium alginate in different concentrations (1, 2 and 4 % w/v) were prepared by soaking accurately weighed quantity of alginate salt in 50ml distilled water and stirring at low speed using an electrical stirrer until homogenous mucilage was formed. To this, Acrycoat E30D, the release controlling polymer was mixed in suitable proportions (0, 2 and 4 % w/w) and the entire mixture was stirred for 30 min. The water insoluble drug, Frusemide, at 30%w/w, was mixed in small portions and dispersed uniformly in the polymer mixture for 15 minutes using electrical stirrer maintaining the speed at 500-600 rpm. The bubble free dispersions were pulled into a glass syringe and extruded thorough a needle (Gauge 17) into a gently agitated 100ml calcium chloride (5% w/v) solution. During extrusion the height of the tip of the needle was maintained at 2cm above the level of the solution, simply by graduating the beaker containing calcium chloride solution, in terms of height, prior to addition of the drug-polymer dispersion. Instantaneous gelation was observed with the formation of wet, heavy calcium alginate micropellets which gradually settles down at the bottom of the beaker. The gelled micropellets were cured or hardened in the calcium chloride solution, which acted as counterion for sodium, for 30 minutes, after the last drop of dispersion was introduced. The white coloured micropellets were then filtered using normal filter paper and washed thoroughly with distilled water to ensure removal of any excess calcium ion adhered on the surface of the wet micropellets. The filtered micropellets were kept in a petri dish over a dry filter paper and dried in open air, so as to soak free water from their surface .They were then dried in hot air oven for 6 hr at 60°C till the wet micropellets got fully dried into non adhering micropellets. The #22 I.P. standard sieve size fractions of the pellets were used for further studies.

A flow sheet of the entire methodology for the preparation of frusemide loaded calcium alginate micropellets is shown in the figure 7.1.

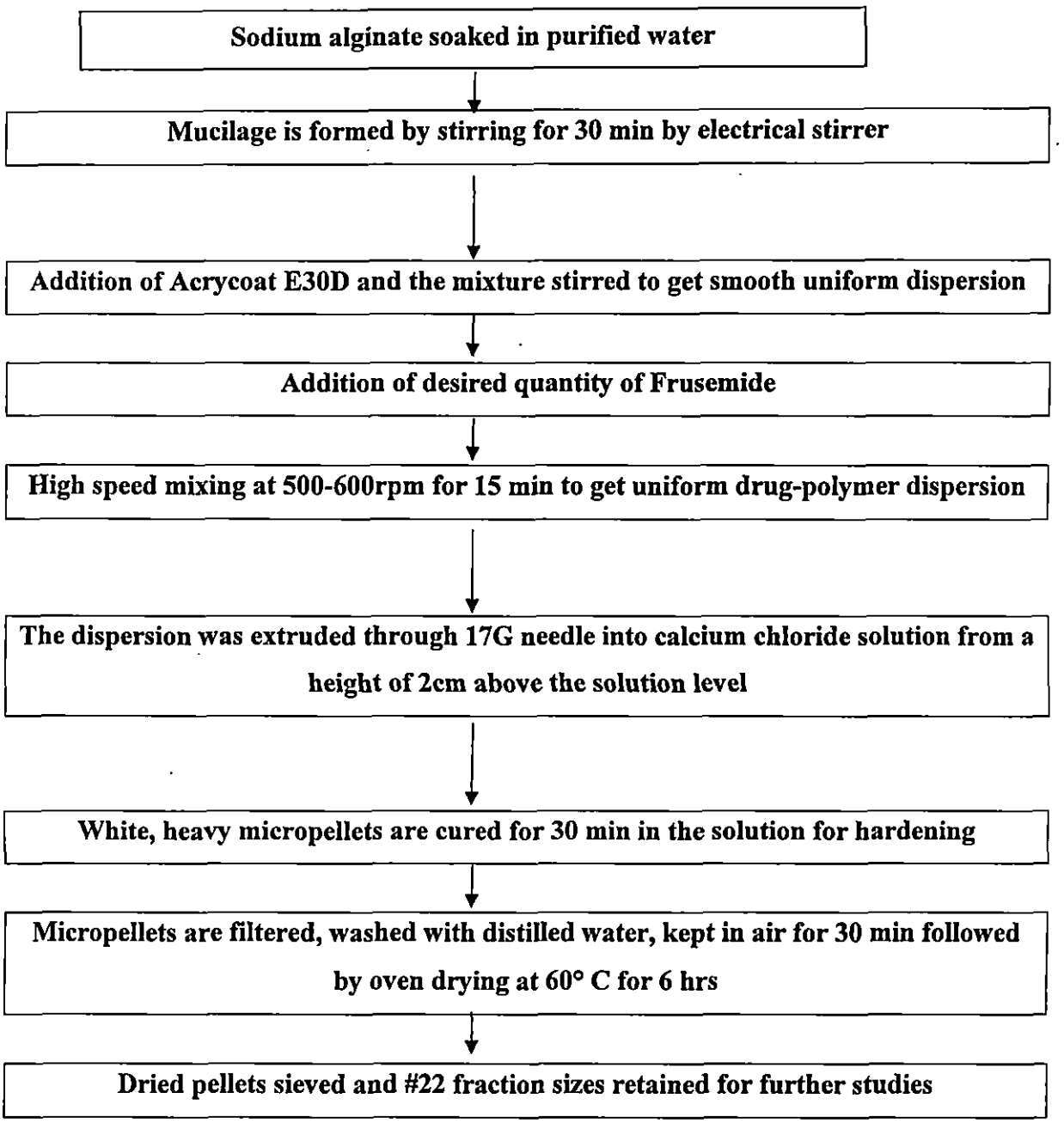

Figure: 7.1 **Flow sheet of the ionotropic gelation method employed for the preparation of frusemide loaded calcium alginate micropellets**

7.6 REFERENCES

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