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STUDIES ON FORMULATION DEVELOPMENT, OPTIMIZATION AND *IN VITRO* RELEASE KINETICS OF PARACETAMOL AND ETODOLAC INDIVIDUALLY AS WELL AS IN COMBINATION FORM

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ABSTRACT

The Present work was for the Formulation of Etodolac, which is practically insoluble in water, and Paracetamol which is sparingly soluble in water, as a single dosage form was a challenging task. The two different approaches were followed, one involving Separate granulation of Etodolac and Paracetamol and then mixing of two granules before compression. The second approach involved combined granulation of Etodolac and Paracetamol. There was light binding done in approach 1 of both granules and in approach 2 there was medium binding. The surfactant was added in both the approaches to aid the dissolution of Etodolac from the combination tablet. Disintegrant was added both intragranularly and extragranularly which enabled good disintegration of the combination tablet. Both the approaches followed were able to give good Disintegration time, Hardness Friability and other parameters of the tablet. Dissolution and Initial Assay values of both Etodolac and Paracetamol were found according to specifications. The three-month stability study samples kept in PVC packs at 25ºC and 60% RH also passes the test for Assay, Dissolution and other physical parameters. So it can be concluded that Etodolac and Paracetamol tablets formulated using both the approaches are good. The combined granulation approach is less time consuming and cost effective.

KEYWORDS

Paracetamol, Etodolac, Granulation Techniques and Poly vinyl chloride.

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INTRODUCTION

Tablets are oral solid dosage forms contains a unit dose of one or more medicaments which are obtained by compression of uniform volumes of powders or granules by applying high pressure using punch and dies. The particles to be compressed consist of one or more medicaments, with or without auxillary substances such as diluents, binders, disintegrants, lubricants, glidants etc. Tablets are the

most convenient and popular dosage form. Tablets can be classified into several categories like uncoated tablets, coated tablets, enteric-coated tablets, dispersible tablets, modified release tablets, effervescent tablets[1-3]. Uncoated tablets may be single layer tablets resulting from a single compression of particles or multiplayer tablets consisting of parallel layers obtained by successive compression of particles of different compositions. No treatment is applied to such tablets after compression.

Coated tablets[4-5] are tablets covered with one or more layers of mixtures of various substances such as resins, gums, inactive and insoluble fillers, sugars, plasticizers, polyhydric alcohols, waxes etc. Coating of tablets helps in masking of the unpleasant taste and odor and the appearance, stability of the appearance, and low hygroscopicity. Most tablets are not composed solely of the drug because drug powders are poorly compressible. Indeed, to ensure good compaction, powders intended for compression into tablets must possess two essential properties: powder flow and compressibility. Most compressed tablets consist of the active ingredient and a diluent (filler), binder, disintegrating agent, and lubricant. Approved FD&C and D&C dyes or lakes (dyes adsorbed onto insoluble aluminum hydroxide), flavors, and sweetening agents may also be present[6-7].

Combination of Etodolac and Paracetamol in a single tablet form is novel combinations. It is formulated as coated tablets. The combination of Paracetamol with Etodolac non-steroidal anti-inflammatory drug (NSAID) offers additive analgesic effect. Concurrent use of paracetamol and an NSAID was superior to paracetamol alone and evidence is found of superior analgesic effect of the combination compared with the NSAID alone.

MATERIAL AND METHOD

MATERIALS

Etodolac and Paracetamol were obtained as a gift samples from Spectrum Pharma, Hyderabad. Lactose Monohydrate, Micro Crystalline Cellulose, Avicel pH 102, Maize Starch, Lactose DCL-11, HPMC K15 M, Mannitol, Polyvinyl Pyrrolidone K 30, HPMC 5 cps, Crossprovidone, Primojel, Talc, Aerosil 200, Magnesium Stearate, Sodium Lauryl Sulphate, Tween 80, Titanium oxide, PEG 6000, Eudragit L100, Iron Oxide Red and Yellow, Cellulose Acetate Phthalate and PEG 400 were obtained as a gift samples from SDFCL, Mumbai. All other chemicals and reagents used were of analytical grade.

METHODOLOGY

Preparation of Etodolac and Paracetamol Tablets

The Label claim for the Tablet consists of Etodolac and Paracetamol was 300mg and 500mg respectively. Two different approaches were followed for the preparation of the tablet in combination (Figure No.1-4). They are as follows:-

EVALUATION PARAMETERS

Preformulation Study of Etodolac and Paracetamol Tablets

Preformulation[8-15] is an exploratory activity that begins early in pharmaceutical development. Preformulation studies are designed to determine the compatibility of initial excipients with the active substance for a biopharmaceutical, physicochemical, and analytical investigation in support of promising experimental formulations. Data from preformulation studies provide the necessary ground work for formulation attempts. Successful formulations take into account a drug's interactions with the physicochemical properties of other ingredients (and their interactions with each other) to produce a safe, stable, beneficial, and marketable product. The basic purpose of the preformulation activity are to provide a rational basis for the formulation approaches, to maximize the chances of success in formulating an acceptable product, and to ultimately provide a basis for optimizing drug product quality and performance. Drug-excipient stability study forms heart of such data. Following receipt of the preformulation information, the formulator may prepare a general summary statement concerning the drug and its properties relative formulation. Before embarking actual experimental run preformulation considerations become important.

Preformulation studies help in the following determinations:

a. Polymorphism
b. Salt Selection
c. Prototype Evaluations
d. Excipient-Excipient Compatibility
e. API-Excipients Interaction Studies
f. pKa Determination
g. Hygroscopicity Studies
h. Phase Solubility Determination
i. Photo stability of API
j. Degradation Pathway Determination
k. Matrix stability evaluations
l. Container-API interactions

All the ingredients have been taken in different ratio with drugs to perform the Preformulation Studies.

REVIEW OF PREFORMULATION STUDIES

The same list of Excipients mentioned above was used for Preformulation study of combined Etodolac and Paracetamol Preformulation study. In the Preformulation study performed here, the excipients were mixed with drugs in the above mentioned ratios and kept in five different conditions which are as follows

- 25°C and 60%RH
- 30°C and 65%RH
- 40°C and 75%RH
- Fridge (below8°C)
- 55°C

The physical observations were noted after 1 month and 2 months. It was found that all the ingredients can be used for the formulations.

RESULTS AND DISCUSSION

PRODUCTS PARAMETERS OF TABLETS OF STABILITY BATCHES

Products Parameters for Approach 1

Description

The Core Tablets were white oval shaped biconvex tablet plain on both sides and the coated tablets were pink colored oval shaped biconvex tablet plan on both sides.

Average Weight

The average weight for the core tablets were 1000mg and for Coated Tablets 1030mg.

Disintegration Time

The disintegration time for the Core and Coated Tablets was 3 and 4 mins. respectively.

Friability

The Friability for the Core Tablets were 0.284%w/w.

Thickness

The thickness for the Core and Coated Tablets was 6.31-6.37 and 6.50-6.58 respectively.

Hardness

The Hardness for the Core and Coated Tablets was 185-205N and 205-230N respectively.

Assay

The Assay value for the Drug Etodolac was 95-105% and for Paracetamol 95-105%.

Dissolution

The Dissolution rate for the Drug Etodolac was 94-101% release in 45 minutes and for the Drug Paracetamol was 95-104% release in 45 minutes.

Products Parameters for Approach 2

Description

The Core Tablets were white to off white oval shaped biconvex tablet plain on both sides and the Coated Tablets were pink colored oval shaped biconvex tablet plan on both sides.

Average Weight

The average weight for the core tablets were 1000mg and for Coated Tablets 1030mg

Disintegration Time

The disintegration time for the Core and Coated Tablets was 5 and 7 mins. respectively.

Friability

The Friability for the Core Tablets were 0.318 % w/w.

Thickness

The thickness for the Core and Coated Tablets was 6.28-6.35mm and 6.50-6.58mm respectively.

Hardness

The Hardness for the Core and Coated Tablets was 190-215N and 205-230N respectively.

Assay

The Assay value for the Drug Etodolac was 91-103% and for Paracetamol 95-102%.

Dissolution

The Dissolution rate for the Drug Etodolac was 91-103% release in 45 minutes and for the Drug Paracetamol was 95-102% release in 45 minutes (Table No.4-5). The Dissolution test for Etodolac and Paracetamol Tablets was performed using 6.8 phosphate buffer as media at speed of 50rpm in paddle type apparatus. For the Formulation of Etodolac which is practically insoluble in water and Paracetamol which is sparingly soluble in water, as a single dosage form was a challenging task. The two different approaches were followed, one involving Separate granulation of Etodolac and Paracetamol and then mixing of two granules before compression. The second approach involved combined granulation of Etodolac and Paracetamol. There was light binding done in approach 1 (Table No.1) of both granules and in approach 2 (Table No.2) there was medium binding. The surfactant was added in both the approaches to aid the dissolution of Etodolac from the combination tablet. Disintegrant was added both intragranularly and extragranularly which enabled good disintegration of the combination tablet.

Stability Study

Once the final formula is arrived at, then the stability batches are prepared, they are packed in different types of packaging and containers, and they are subjected to three different conditions (Table No.3).

- Room Temperature (25°C and 60% Relative Humidity).
- 30°C and 65% Relative Humidity.
- 40°C and 75% Relative Humidity.

For periods of 1, 2, 3, 6, 9, 12, 18, 24 and 36 months as may be the case applicable. These are in line with ICH guidelines.

Stability testing is a routine procedure performed on drug substances and products. It is involved at various stages of product development. In early stages, accelerated stability testing (at relatively high temperatures and/or humidities) can be used as a "worst case" evaluation to determine what types of degradation products may be found after long-term storage. Testing under more gentle conditions (those recommended for long-term shelf storage), and slightly elevated temperatures, can be used to determine a product's shelf life and expiration dates. In these types of studies, the product is analyzed at intervals for various parameters, which may include assay of the active ingredient, measurement of known degradation products, dissolution time, appearance, etc.

Table No.1: Stability Testing Data for Individual Granulation Approach

S.No	Batch Number	Diluent (%)	Disintegrant (%)	Binder (%)	Surfactant (%)	Lubricant (%)	Preservative (%)
1	1	1.2	11.5	0.6	0.3	0.5	0.08
2	2	1.2	11.5	0.6	0.3	0.5	0.08
3	14	0.6	16	1	0.8	0.8	0.09
4	19	0.6	16	1	0.8	0.8	0.09
5	20	0.6	16	1	0.8	0.8	0.09

Table No.2: Stability Testing Data for Combined Granulation Approach

S.No	Batch Number	Diluent (%)	Disintegrant (%)	Binder (%)	Surfactant (%)	Lubricant (%)	Preservative (%)
1	3	3.7	12	2	1	1	0.1
2	4	2.8	14	1	1	1	0.1
3	5	1	15.5	1.5	1	1	0.1
4	6	1	15.4	1.5	1	1	0.1
5	7	1	14.5	2	1.5	1	0.09
6	13	0.7	14.25	2	1.5	0.8	0.09
7	17	0.7	14.25	2	1.5	0.8	0.09
8	18	0.7	14.25	2	1.5	0.8	0.09

Table No.3: Conditions of stability testing

S.No	Storage Temperature (°C)	Relative Humidity (%)	Minimum Time period covered by data at submission (months)
1	Accelerated: 40±2	75±5	6
2	Intermediate: 30±2	65±5	12
3	Long term: 25±2	60±5	12

Table No.4: Data of Assay and Dissolution Values for Individual Granulation approach

S.No	Test	Specification	Batch No.	Initial	After 1 month	After 2 months	After 3 months
1	Dissolution	Etodolac: NLT 70% in 45 minutes	14	95.11-100.16%	96.34-98.91%	94.61-99.44%	84.64-91.68%
			19	86.47-97.14%	92.12-100.58%	90.47-102.69%	97.66-101.85%
			20	100.10-110.41%	95.91-97.97%	97.09-101.03%	96.40-101.58%
		Paracetamol: NLT 70% in 45 minutes	14	97.75-104.75%	97.50-100.43%	96.80-98.62%	93.69-98.13%
			19	89.70-102.31%	89.59-99.14%	92.28-100.69%	96.46-101.64%
			20	95.43-103.58%	96.89-98.79%	99.96-100.81%	96.91-101.41%
2	Assay	Etodolac: 95.0%-105%	14	99.88%	99.63%	100.80%	98.19%
			19	99.65%	101.39%	100.92%	99.93%
			20	100.53%	100.60%	100.48%	100.13%
		Paracetamol: 95.0%-105%	14	99.68%	99.88%	99.90%	99.23%
			19	100.20%	99.69%	99.23%	99.60%
			20	99.92%	100.99%	100.96%	100.79%

Table No.5: Data of Assay and Dissolution Values for Combined Granulation approach

S.No	Test	Specification	Batch No.	Initial	After 1 month	After 2 months	After 3 months
1	Dissolution	Etodolac: NLT 70% in 45 minutes	13	91.73-102.29%	89.29-99.58%	94.30-97.64%	87.81-100.25%
			17	98.16-101.15%	98.80-101.04%	90.42-96.44%	98.42-101.06%
			18	88.98-98.16%	96.84-100.34%	83.71-93.87%	97.00-99.80%
		Paracetamol: NLT 70% in 45 minutes	13	96.36-101.02%	90.03-95.50%	93.75-95.30%	95.84-102.27%
			17	97.85-102.48%	96.48-101.40%	96.39-98.84%	96.42-98.70%
			18	94.58-102.34%	98.44-99.78%	98.18-92.40%	94.14-99.66%
2	Assay	Etodolac: 95.0%-105%	13	100.38%	98.26%	101.16%	99.77%
			17	99.52%	100.78%	98.75%	100.41%
			18	99.56%	101.17%	98.37%	99.69%
		Paracetamol: 95.0%-105%	13	99.65%	99.31%	99.52%	99.85%
			17	98.28%	101.01%	100.53%	100.45%
			18	100.52%	101.60%	101.47%	101.61%

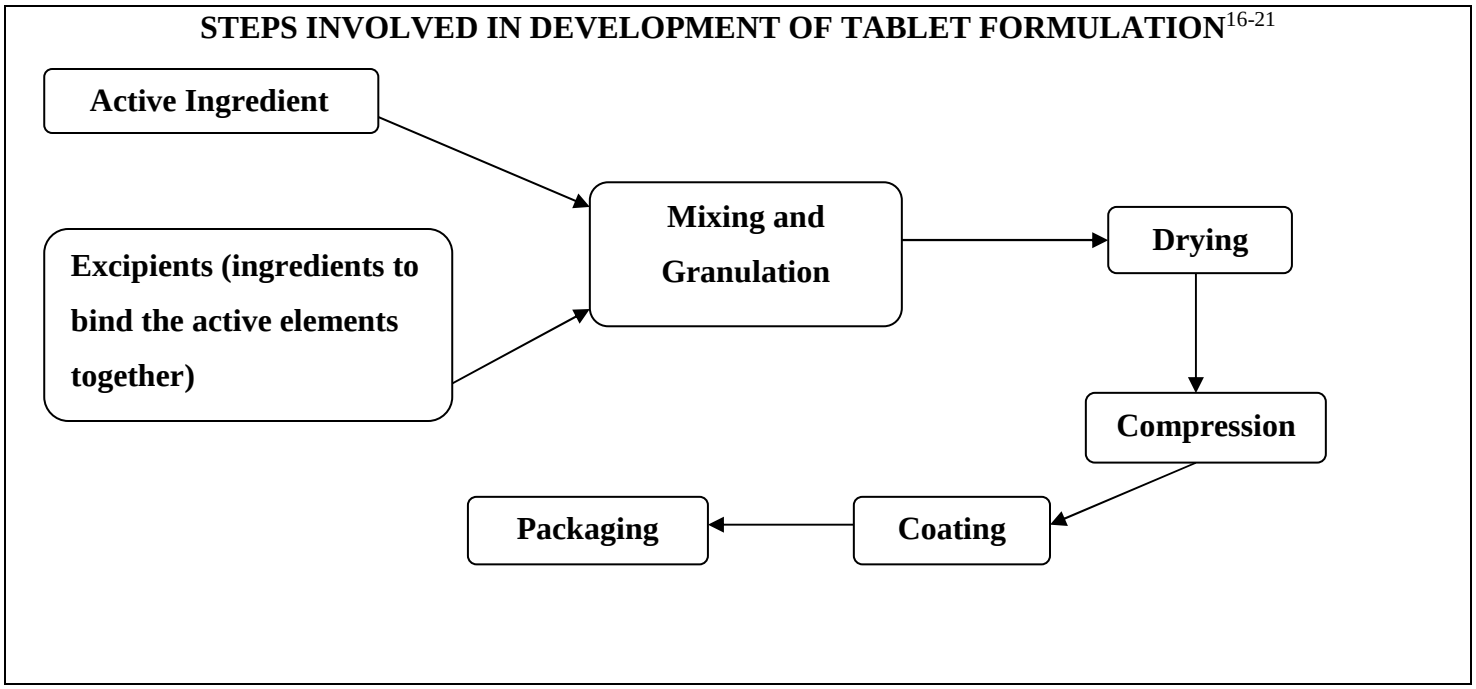

Figure No.1: Steps involved in the development of tablets formulations

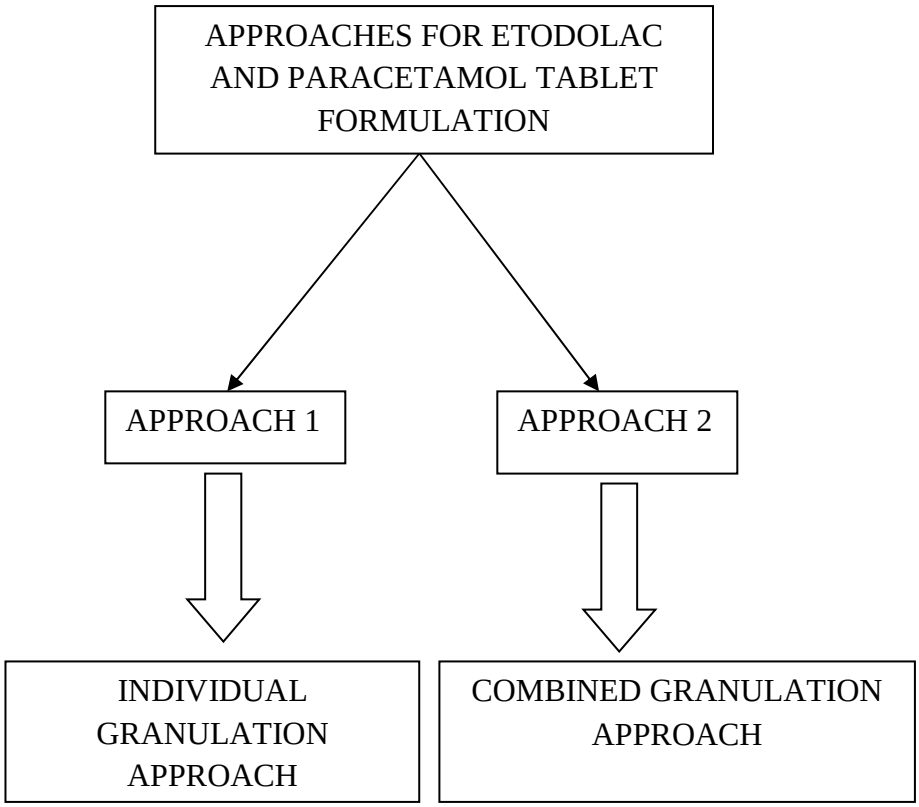

Figure No.2: Different approach for the Formulations

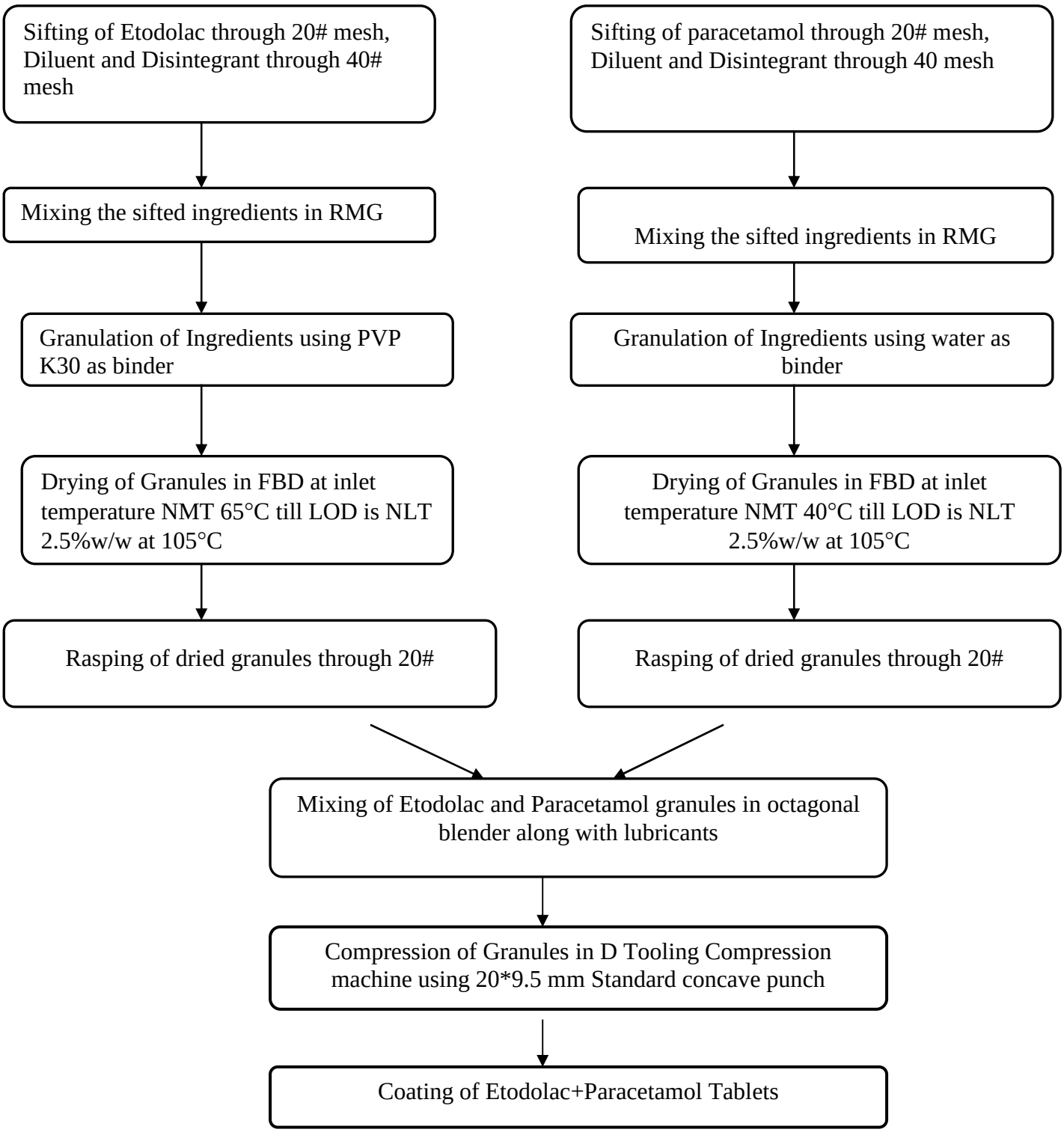

Figure No.3: Individual Granulation Approach (APPROACH - 1)

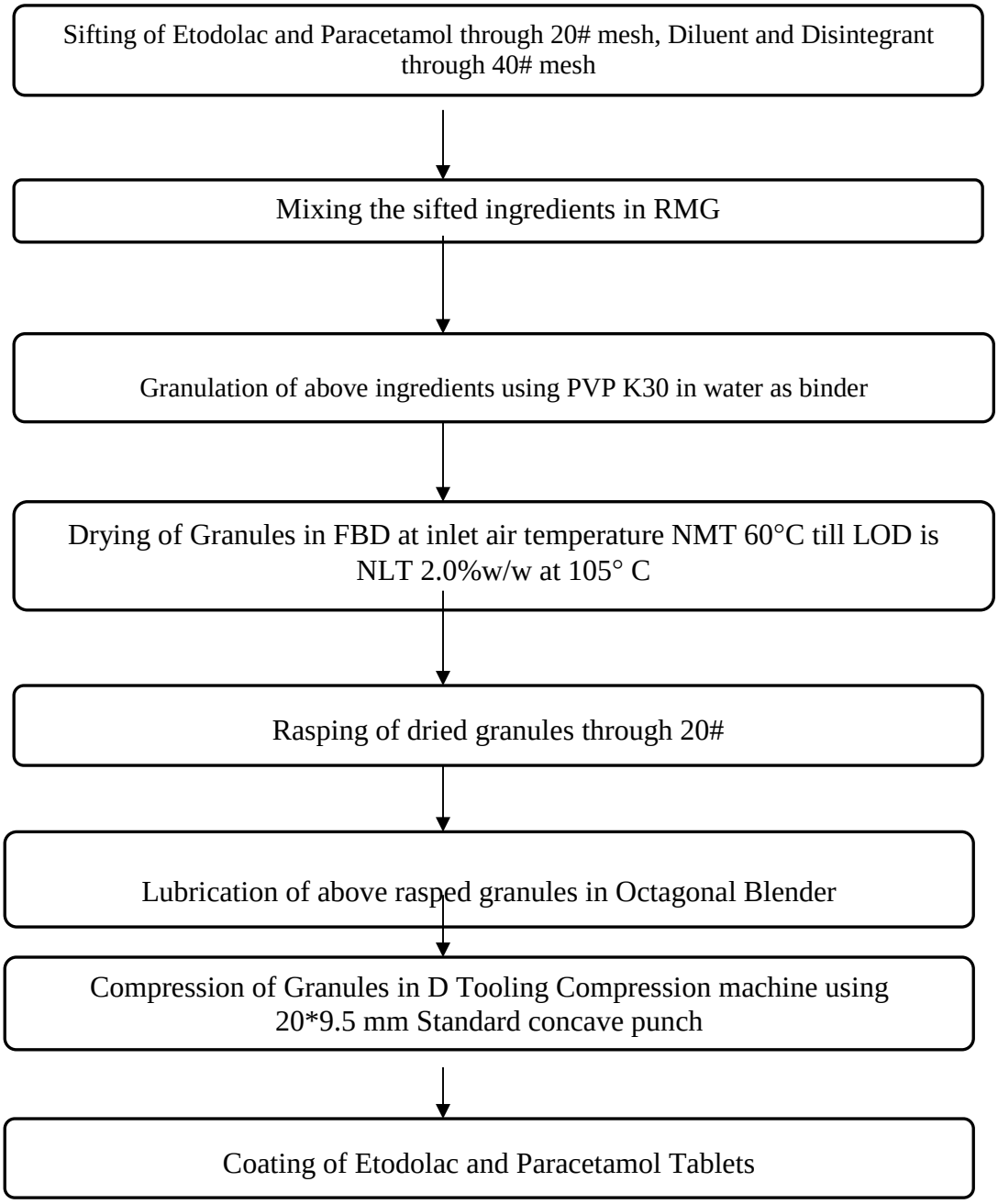

Figure No.4: Combined Granulation Approach (APPROACH - 2)

CONCLUSION

Both the approaches followed were able to give good Disintegration time, Hardness Friability and other parameters of the tablet. Dissolution and Initial Assay values of both Etodolac and Paracetamol were found according to specifications. The three-month stability study samples kept in PVC packs at 25ºC and 60% RH also passes the test for Assay, Dissolution and other physical parameters. So it can be concluded that Etodolac and Paracetamol tablets formulated using both the approaches are good. The combined granulation approach is less time

consuming and cost effective, so this approach will be used for launch of Etodolac and Paracetamol Tablets in the Market.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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