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Use of Ternary Diagram in Formulation Design of Paracetamol Tablets

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Abstract

The development of a drug into a stable and marketable product involves many stages and processes using various equipment and experimental designs, and these have taken a toll on the cost and time it takes to produce such products. It will be desirable to develop a process that can shorten the time and cost using minimal facility. The ternary diagram was used to develop such a tool chart that could be used to study the effect of formulation factors; binder, disintegrant and compression pressure on tablet properties with a view to predicting tablet characteristics. The values of each factor (less than to greater than the maximum used in tablet formulations) were plotted along each axis of the three sides of the ternary diagram. Points were selected randomly within the ternary diagram to obtain concentrations or values to be used for each factor in tablet formulation. Paracetamol tablets (500 mg) were formulated by wet granulation to give a total tablet weight of 700 mg. The tablets were evaluated for friability, hardness, disintegration time and weight variation. Regions on a ternary diagram that produced tablets batches that passed disintegration time test were delineated as satisfactory while those that failed were delineated as unsatisfactory. Subsequently, new tablet batches were formulated according to values of selected points along tie-lines drawn across satisfactory and unsatisfactory regions on two sides of the diagram. The tablets were evaluated for tablet properties in which results showed that tablets batches made from satisfactory regions passed while those from unsatisfactory regions failed. Thus ternary diagram could be used as a tool to select formulation factor values for making acceptable tablets.

1 Introduction

The development of a new pharmaceutical excipient into a stable and marketable product is usually a long process, incurring high cost and waste of materials. A property-based design with supporting pre-formulation data is used to direct formulation efforts in order to give active ingredients the highest possibility of success as a dosage form. Such property based designs have been used for pro-drug design, active-ingredient-based design, pre-formulation excipient selection and formulation compatibilities[1]. Experimental designs have been optimized using mathematical models[2] and when combined graphically and mathematically, used to determine satisfactory compositions of ingredients in formulations. Other workers [3, 4, 5] have used computer software generated models with statistics to predict, observe and design formulations of suitable compositions.

Optimization is useful for screening, factor studies and for best formula or process determination. Screening studies are used to identify factors that influence the formulation or process while statistical design can be used for assessing stability and compatibility[6]. Experimental designs have been described using factors at two levels[7], however, there are other designs at 3, 4 and 5, though the 2 or 3 factors interaction's studies were found to be more important than higher-order interactions[6]. Optimization of the formula and/or process using mathematical models are important because formulations consist of mixtures of the active ingredient with excipient and the quality of the formulation depends largely on the proportion of the constituent

rather than the quantity of each in the formulation[8,9]. Therefore the peculiar properties which screening and factor studies may not identify would require mixture studies and ternary diagram have been used for such design studies[6].

Factor studies are useful for identifying quantitatively the influence of different factors together on the response variables. Therefore, the effect of design variables to the response and the presence of interactions between the design variables can be studied[10, 11]. Factorial designs enable the determination of the influence over the factors when subjected to statistical analysis.

Ternary diagram design for tablet formulations involves the use of little technological input, it is fast enough without wasting time of researcher which meets the needs of many researchers with funding and facilities challenges. Ternary diagrams have been used in pharmaceutical formulation designs to describe experimental domains[12] to optimize excipient blends[13], to design and evaluate novel formulations[14] and to determine primary formulation components during screening and optimization method[15]. They have not been used to determine satisfactory regions of Paracetamol tablet formulations as a means to determine levels of excipients in the formulation.

2 Materials and Methods

2.1 Materials

Maize starch and paracetamol powder were purchased from Tianjin Henxin Pharm., China. Gelatin powder, magnesium stearate (BDH Chem. Ltd. Poole, England), heavy magnesium carbonate (Gurr Chem, Belss and sons, England) and talc powder (Searle Co, Hopkin and William Chadwell Health Essex, England).

2.2 Methods

2.2.1 Formulation of ternary diagram (TD) batches

The “low” and “high” values of gelatin, maize starch and compression pressure that have been determined in earlier study[16] were fitted into the ternary diagram (Fig 1) in which values outside, and within the “low” and “high” levels were accommodated on the scales. Various points were randomly selected on the ternary diagram to formulate 700 mg paracetamol tablets containing 500 mg paracetamol prepared by wet granulation (Table 1).

2.2.2 Determination of tablet friability, hardness and disintegration time of TD batches

Each tablet batch was subjected to friability (Erweka Friabilator TA 3R, Germany), hardness (Monsanto Hardness Tester, CT Engineering, England) and disintegration time (Eagle Scientific Disintegration Apparatus, England) tests as described by official book and various workers.[17-20]

2.2.3 Formulation and Evaluation of Tie - Line Batches

Points were selected from fig 1 that produced satisfactory region of disintegration time and delineated as satisfactory while those that failed were designated as unsatisfactory regions of tablet disintegration time on the ternary diagram. A tie-line was drawn through both regions on two sides along which six points were randomly selected to prepare new tablet batches (Table 2). Tablet friability, hardness and disintegration time of the tie-line batches were similarly evaluated as above. Other tablet properties evaluated included dissolution rate, tensile strength and binding capacity.

Batches within a satisfactory region of disintegration time on both Tie-lines; XX^1 and BB^1, had satisfactory friability, disintegration time and hardness values. All other batches failed these tests being outside satisfactory regions of tablet disintegration time. Some changes occurred progressively along the two tie-lines which can be summarized as follows:

Fig 2 shows the relationship between binder concentration and pressure that would produce satisfactory tablets when disintegrant concentration is kept constant (Tie-line XX^1).

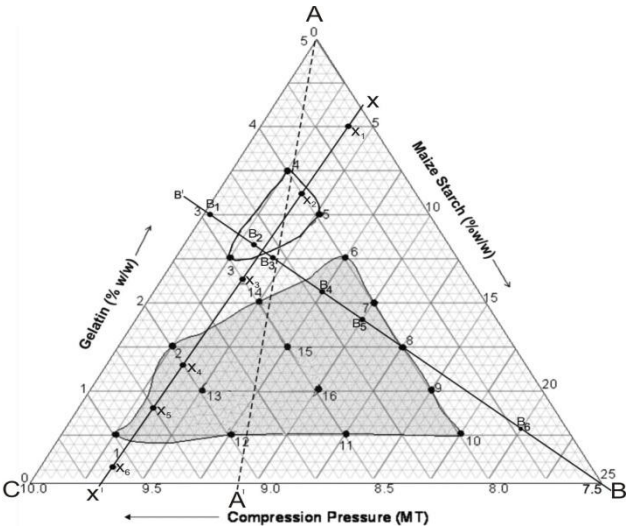

Fig 1: Satisfactory and unsatisfactory region of tablet disintegration time with tie-lines passing through satisfactory (≤ 15 min) and unsatisfactory (≥ 15 min) regions for tablet disintegration time.

Shaded area - Satisfactory region of tablet disintegration time; Unshaded area - Unsatisfactory region of tablet disintegration time

Fig 3 shows how binder concentration should vary to produce satisfactory tablets when the ratio of compression pressure and disintegrant are kept constant (Tie-line BB^1). The release characteristics of tablets along tie-lines are presented in table 5 in which the result shows that $t_{50\%}$ range from 8 to 43 min and C_{max} from 42 to 99 %.

4 Discussions

Tablet properties are affected mainly by the excipients used especially the binders, disintegrants[10,11] and lubricants[22] in terms of types and quantity, in addition to compression pressure[23]. From table 3, binder and compression pressures

were shown to influence disintegration time. The result of changes in the three factors along tie-line formulation XX^1 batches showed that if disintegrant concentration is kept constant along XX^1 while decreasing binder concentration, compression pressure must increase to produce satisfactory tablets (Fig 2).

If the proportional ratio of compression pressure and binder concentration is to be kept constant along BB^1, satisfactory tablets are better produced by increasing disintegrant concentration. Some situations may necessitate having an appropriate ratio of binder: compression pressure, otherwise excessive binder content may produce very hard granules that may not be properly compressed at a given compression pressure. It was not possible to construct a tie-line that will keep binder concentration constant, or keeping the ratio of binder: disintegrant constant, because such tie-lines would not transverse both satisfactory and unsatisfactory regions.

Table 1: Formulae for preparing 200 tablets per batch for 700 mg tablet weight using values of binder, disintegrant and compression pressure obtained from selected points on ternary diagram

Ternary points from Fig.1	PCM Powder (g)	M/S (g) (% value from Ternary diagram)	Heavy $MgCO_3$ (g)	Gelatin (g) (% value from Ternary diagram)	Talc (g)	Mg stearate (g)	CP obtained from ternary diagram (MT)
1	100	3.5 (2.5)	32.86	0.7 (0.5)	2.8	0.14	9.5
2	100	3.5 (2.5)	31.46	2.1 (1.5)	2.8	0.14	9.0
3	100	3.5 (2.5)	30.06	3.5 (2.5)	2.8	0.14	8.5
4	100	3.5 (2.5)	28.66	4.9 (3.5)	2.8	0.14	8.0
5	100	7.0 (5.0)	25.86	4.2 (3.0)	2.8	0.14	8.0
6	100	10.5 (7.5)	23.06	3.5 (2.5)	2.8	0.14	8.0
7	100	14.0 (10.0)	20.26	2.8 (2.0)	2.8.	0.14	8.0
8	100	17.5 (12.5)	17.46	2.1 (1.5)	2.8	0.14	8.0
9	100	21.0 (15.0)	14.66	1.5 (1.0)	2.8	0.14	8.0
10	100	24.5 (17.5)	11.86	1.4 (1.0)	2.8	0.14	8.0
11	100	17.5 (12.5)	18.86	0.7 (0.5)	2.8	0.14	8.0
12	100	10.5 (7.5)	25.86	0.7 (0.5)	2.8	0.14	8.5
13	100	7.0 (5.0)	28.66	1.4 (1.0)	2.8	0.14	9.0
14	100	7.0 (5.0)	27.26	2.8 (2.0)	2.8	0.14	9.0
15	100	10.5 (7.5)	24.46	2.1 (1.5)	2.8	0.14	8.5
16	100	14.0 (10.0)	21.66	1.4 (1.0)	2.8	0.14	8.5

PCM - Paracetamol powder; M/S - maize starch; heavy$MgCO_3$. heavy magnesium carbonate; M/stearate - magnesiumstearate;
CP - c ompression pressure; MT- Metric Tonnes.

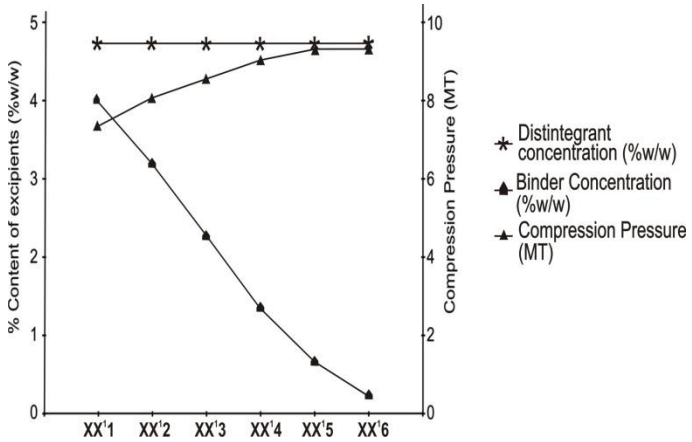

Fig 2: Tie-line XX^1 formulations showing how the three factors change in moving from unsatisfactory to satisfactory regions of disintegration time.

Note:Batches XX^1 4 and 5 were from satisfactory regions of Figure 1; All other batches were from unsatisfactory regions of Figure 1.

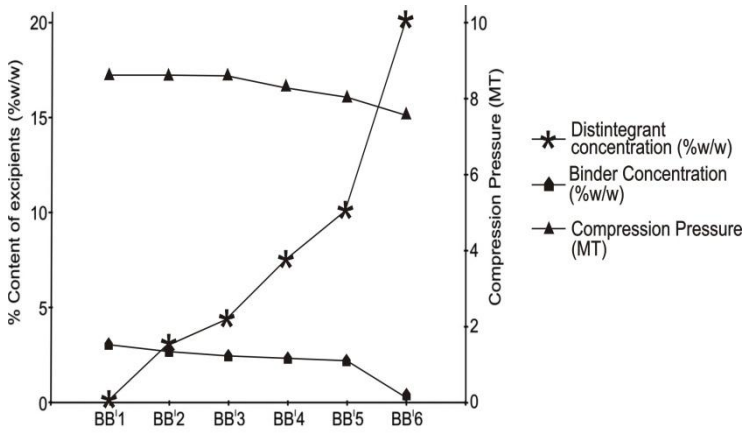

Fig 3: Tie-Line BB[1] formulations showing how the three factors change in moving from unsatisfactory to satisfactory regions of disintegration time.

Note: Batches BB[1] 4 and 5 were from satisfactory regions of Figure 1; All other batches were from unsatisfactory regions of Figure 1

Table 2: Formulae for 200 tablets for the various batches for 700 mg tablet weight using values of binder, disintegrant and compression pressure obtained from tie-lines XX[1] and BB[1] passing from satisfactory to unsatisfactory regions of tablet disintegration time

Batch No	PCM (g)	M/S (g) (% value from Tie-line)	Heavy $MgCO_3$ (g)	Gelatin (g) (% value from Tie-line)	Talc (g)	Mg/St (g)	CP value from Tie-line (MT)
$XX^1$1	100	6.79 (4.85)	24.67	5.6 (4.0)	2.8	0.14	7.5
$XX^1$2	100	6.79 (4.85)	25.79	4.48 (3.2)	2.8	0.14	8.0
$XX^1$3	100	6.79 (4.85)	27.12	3.15 (2.25)	2.8	0.14	8.5
$XX^1$4	100	6.79 (4.85)	28.45	1.82 (1.3)	2.8	0.14	9.0
$XX^1$5	100	6.79 (4.85)	29.01	1.26 (0.9)	2.8	0.14	9.5
$XX^1$6	100	6.79 (4.85)	29.99	0.28 (0.2)	2.8	0.14	9.5
$BB^1$1	100	0.7 (0.5)	32.16	4.2 (3.0)	2.8	0.14	8.5
$BB^1$2	100	4.2 (3.0)	29.08	3.78 (2.7)	2.8	0.14	8.5
$BB^1$3	100	6.3 (4.5)	27.26	3.5 (2.5)	2.8	0.14	8.5
$BB^1$4	100	10.08 (7.5)	23.76	2.8 (2.0)	2.8	0.14	8.0
$BB^1$5	100	14.0 (10.0)	20.56	2.5 (1.8)	2.8	0.14	8.0
$BB^1$6	100	28.0 (20.0)	8.22	0.84 (0.6)	2.8	0.14	7.5

PCM - Paracetamol powder; M/S - maize starch; heavy$MgCO_3$. heavy magnesium carbonate; M/stearate - magnesiumstearate; CP - compression pressure; MT- Metric Tonnes

A construction of another tie-line AA^1 to line BC would give a constant ratio of disintegrant: compression pressure, from where it can be seen that binder concentration should be reduced to produce satisfactory tablets. This was explained by the interaction between Disintegrant (B) and compression pressure (C) on disintegration time.[16] The additive effect can be reduced by reducing binder concentration so as not to produce excessively hard tablets. The release characteristics of tablets from tie-lines XX^1 and BB^1 show that four batches, $XX^1$1, $BB^1$1, $BB^1$2 and $BB^1$3 did not release up to 50 % of their drug content at the end of 60 min. All these batches were from outside regions of satisfactory tablet disintegration time. Batches $XX^1$2, $XX^1$3, $XX^1$6 and $BB^1$6 though from outside regions of satisfactory tablet disintegration time, had maximum release values of 70, 54, 70 and 100 % respectively after 60 min. Batches made from regions of satisfactory disintegration time, $XX^1$4, $XX^1$5, $BB^1$4 and $BB^1$5 had maximum release values of 80, 60,70, and 95 % after 60 min. respectively. This result could be attributed to the role of deceasing binder concentration in the release profile of formulations along XX^1 and increasing disintegrant concentrations along BB^1. Though $XX^1$6 and $BB^1$6 were from an outside satisfactory region of disintegration time, their drug release profile can be explained by the low binder concentration and high concentration of disintegrant for $XX^1$6 and $BB^1$6 respectively, and especially for $BB^1$6, the low compression pressure contributed to the 100 % drug release. The lower release by batches $XX^1$5 (64%) and $BB^1$4 (71%) could be attributed to the higher compression pressures used[23]

and the quantity or proportions of binder and disintegrant[10,11, 23] in which $XX^1$5 was compressed at 9.5MT and $BB^1$4 contained 2.0% binder concentration, which was less than for $XX^1$6 (0.2%) and $BB^1$6 (0.6%) Authors have reported the influence of ratio and the proportions of binder and disintegrant concentrations to influence tablet release[5,16].

Table 3: Some physical properties of tablet batches made from various selected points on ternary graph

Batch	Mean DT (min) ± SD, n = 3	Mean friability (%) ± SD, n = 5	Mean hardnes (KgF) ± SD, n= 10	Mean tablet weight (g) ± SD, n = 20
1	0.6 ± 0.023	17.73 ± 0.001	6.7 ±0.12	0.564±0.040
2	05.0 ± 0.021	25.77 ±0.00	5.5 ± 0. 12	0.647±0.038
3	30.0 ± 0.021	1.13 ±0.001	13.5 ±0.11	0.680±0.013
4	30.0 ± 0.023	1.14 ±0.000	13.5 ± 0.11	0.646±0.030
5	28.2 ± 0.023	1.14 ±0.000	13.5 ±0.12	0.673±0.030
6	0.6 ± 0.021	2.01 ±0.000	6.4 ± 0.12	0.667±0.031
7	0.6 ± 0.022	2.40 ±0.001	9.3 ±0.11	0.676±0.029
8	0.6 ± 0.022	2.50 ±0.001	9.2 ±0.11	0.640±0.012
9	0.5 ± 0.022	2.57 ±0.002	6.6 ±0.12	0.652±0.028
10	0.6 ± 0.023	10.70 ±0.001	3.0 ±0.11	0.624±0.019
11	0.3 ± 0.021	2.57 ±0.001	7.7 ±0.13	0.746±0.017
12	0.4 ± 0.021	1.51 ±0.000	8.7 ±0.12	0.655±0.063
13	0.5 ± 0.023	1.31 ±0.000	9.4 ±0.13	0.688±0.023
14	1.3 ± 0.021	0.95 ±0.001	13.5 ±0.11	0.654±0.030
15	0.5 ± 0.023	1.36 ±0.002	13.5 ±0.12	0.651±0.006
16	0.4 ± 0.021	1.12 ±0.002	13.5 ±0.11	0.655±0.017

DT - disintegration time; Min – minutes; SD - Standard deviation; n - Number of times experiment was carried out

Table 4: Tablet properties of obtained along tie-lines XX^1 and BB^1 moving from satisfactory to unsatisfactory regions of disintegration time on a ternary diagram

Batch	Mean DT (min) ±SD, n=3	Mean friability (%) ±SD, n=5	Mean hardness (KgF) ±SD, n=10	TS (MNm^{-2}) x10 $^{-1}$	BC (Nm^{-1}) x10^{-2}	Tablet thickness (m) x10 $^{-3}$	CP (MT)	Tablet weight* (g) ± SD n = 20
$XX^1$1	30.0±0.0	0.74±0.05	13.5±0.0	12.89	2.53	5.33	7.5	0.688±003
$XX^1$2	21.00±0.05	1.60±0.05	10.8±0.10	10.05	1.87	5.47	8.0	0.685±0.008
$XX^1$3	30.0±0.0	1.60±0.04	13.5±0.0	12.50	2.45	5.50	8.5	0.738±0.007
$XX^1$4	14.17±0.02	1.50±0.05	09.5±0.11	08.59	1.69	5.63	9.0	0.710±0.008
$XX^1$5	13.00±0.02	1.90±0.05	09.0±0.12	08.36	1.64	5.48	9.3	0.723±0.012
$XX^1$6	04.00±0.01	1.90±0.05	06.8±0.11	06.34	1.25	5.46	9.5	0.721±0.041
$BB^1$1	30.0±0.0	0.54±0.0.05	13.5±0.0	12.52	2.46	5.49	8.5	0.728±0.002
$BB^1$2	30.00±0.0	1.30±0.04	13.5±0.0	12.57	2.47	5.47	8.3	0.702±0.005
$BB^1$3	30.00±0.0	1.40±0.03	13.5±0.0	12.89	2.53	5.33	8.3	0.695±0.003
$BB^1$4	14.00±0.01	1.60±0.05	09.0±0.11	08.71	1.73	5.26	8.2	0.684±0.003
$BB^1$5	00.60±0.01	2.00±0.03	08.0±0.12	07.34	1.44	5.55	8.2	0.686±0.005
$BB^1$6	00.50±0.01	8.40±0.06	03.6±0.130	02.83	0.56	6.47	7.7	0.656±0.005

DT - disintegration time; Min – minutes; SD - Standard deviation; n - Number of times experiment was carried out; TS - ensile strength; BC - Binding capacity

Batch $XX^1$4 had a better release profile than batch $XX^1$5 and $BB^1$4 as a result of the lower pressures used in its compaction. Other mechanisms may also be at play for drug release other than tablet disintegration, indeed drug release mechanisms may

be complex processes involving swelling, erosion and diffusion across tablet surfaces[24, 25].

Table 5: Release characteristics of tablet batches made from tie-lines XX^1 and BB^1

Batch No	$t_{50\%}$ (min.)	C_{60mins} (%)	CP (MT)
$XX^1$1	-	48	7.5
$XX^1$2	14	71	8.0
$XX^1$3	43	54	8.5
$XX^1$4	20	81	9.0
$XX^1$5	26	64	9.5
$XX^1$6	25	71	9.5
$BB^1$1	-	44.5	8.5
$BB^1$2	-	42	8.5
$BB^1$3	-	43	8.5
$BB^1$4	23	71	9.5
$BB^1$5	8	95	8.0
$BB^1$6	8.5	99	7.5

5 Conclusions

If disintegrant concentration is kept constant along XX^1 while decreasing binder concentration, compression pressure must increase to produce satisfactory tablets (Fig 2). If the proportional ratio of compression pressure and binder is to be kept constant along BB^1, satisfactory tablets are better produced by increasing disintegrant concentration (Fig 3). Some situations may necessitate having an appropriate ratio of binder: compression pressure, otherwise excessive binder content may produce very hard granules that may not be properly compressed at a given compression pressure.

A construction of another tie-line from apex A to line BC (fig 1) to produce AA^1 tie-line would give a constant ratio of disintegrant: compression pressure, from where it was observed that binder concentration should be reduced to produce satisfactory tablets. This was reported[16] to be due to the interaction between disintegrant (B) and compression pressure (C) on disintegration time. This additive effect can be minimized by reducing binder concentration so as not to produce excessively hard tablets.

The developed tool chart makes it possible to draw any tie-line formulator desires from unsatisfactory to satisfactory regions of the ternary diagram and to choose factor levels within the satisfactory region when good tablets could be formulated.

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7 Conflict of interest

The authors hereby declare that they have no competing interests

8 Authors contributions

JDAP and MAI designed the work, JDAP carried out literature review, bench work and preparation. Both authors read and approved the final manuscript

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