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EFFECT OF BINDER TYPE AND CONCENTRATION ON PHYSICAL AND IN VITRO PROPERTIES OF DICLOFENAC POTASSIUM 50MG TABLET

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ABSTRACT

The aim of this study is to investigate the effect of different binder types on the pharmaceutical properties of Diclofenac potassium tablets. Nine formulation runs were prepared using 3 binders: Microcrystalline cellulose 101 (Vivapur® 101), Pregelatinized starch (Lycatab®) and Maize starch. Each used in 3 different concentrations (15%, 35% and 55%).All the formulation runs were subjected to weight variation, hardness, friability, disintegration time and dissolution tests. The results have shown that different binders with different concentrations will result in different weight variation, hardness, friability, disintegration time and dissolution profile (drug release).From this study it has been concluded that using maize starch as a binder with 35% concentration led to the best physical properties with acceptable dissolution profile regarding similarity with the originator (Cataflam®).

KEYWORDS: Diclofenac potassium, binder type, binder concentration, dissolution profile, similarity factor.

INTRODUCTION

Oral route is the most common used route for drug administration. The most popular form for oral drug delivery is the tablets[1], which are one of the most convenient drug administration routes for the patients and they are usually easy to handle and identify.[1,2]

Tablets are commonly manufactured by one of the following manufacturing processes: Direct compression, Wet granulation and Dry granulation methods.[3] Direct compression is highly efficient, less laborious and increasingly becoming more popular than both compression granulation and wet granulation methods in the manufacturing of tablets. However, few drug powders can be manufactured by the direct compression method, while most drugs need the incorporation of other excipients in order to achieve satisfactory properties such as strength, disintegration and dissolution times. One such excipient is the binding agent.[4]

Binding agents are used to impart cohesive qualities to the powdered material. They impart a cohesiveness to the tablet formulation that ensures the tablet remaining intact after compression, as well as improving the free-flowing qualities by the formulation of granules of desired hardness and size.[5]

Binders are usually selected on basis of previous experience, particular product needs, literature or vendor data or the preference of individual scientists or manufacturing unit. The primary criterion when choosing a binder is its compatibility with other tablet components.
The dominating bonding types which adhere particles together in a tablet made of dry powders by direct compression are considered to be distance attraction forces, solid bridges and mechanical interlocking.[6]

In tablet formulation the binder and disintegrant are critical ingredients that influence the dissolution rate of drugs from tablets.[7] Several studies reported[8-13]

A model-independent mathematical method was developed by Moore and Flanner for comparison of dissolution profiles using two factors, f1 and f2. The factor f2, known as the similarity factor, measures the closeness between two profiles.[14]

This study evaluates the effect of three different binders and their levels, using general factorial design by considering the type and level of binder as two factors at three levels (32).Nine formulation runs were prepared with 3 binders: Microcrystalline cellulose 101 (MCC 101), Pregelatinized starch (PGS) and Maize starch. Each used in 3 different concentrations (15%, 35% and 55%).

Diclofenac potassium, an important non-steroidal anti-inflammatory drug (NSAID), was chosen in the present study due its poor compressibility.[4]

MATERIALS AND METHODS

Materials

Diclofenac potassium (Diclofenac potassium USP, Amoli Organics, India) tablets were prepared using 3 different binders: maize starch type B (Roquette, France), microcrystalline cellulose (Vivapur® 101, JRS Pharma, Germany) and pregelatinized starch (Lycatab® PGS, Roquette, France). The rest of the materials used were dibasic calcium phosphate (Budenheim, Germany), sodium starch glycolate (Explotab®, JRS Pharma, Germany) povidone k30 (Shanghai Yuking, China), colloidal silicon dioxide (Aerosil®, Anatwerpen, Germany) and magnesium stearate (Peter Greven, Netherland).

Chemical reagents used were sodium hydroxide (Scharlau, Spain) and potassium monobasic phosphate (Duksan, Korea).

2.2 Experimental design

Design Expert (V8.0.6) program was used to design the experiment by using general factorial design (32). The program gave nine randomized formulae (F1-F9), which were all formulated by direct compression as shown in table 1.

Table 1: Experimental runs layout for the 32 fractional factorial design.

Composition / Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diclofenac potassium	50mg	50mg	50mg	50mg	50mg	50mg	50mg	50mg	50mg
Pregelatinized starch	15%	0%	0%	0%	35%	0%	0%	55%	0%
Maize starch	0%	35%	0%	0%	0%	55%	0%	0%	15%
MCC 101	0%	0%	55%	15%	0%	0%	35%	0%	0%

Sodium starch glycolate, povidone, colloidal silicon dioxide and magnesium stearate were all used with fixed concentrations in all the formulas, where dibasic calcium phosphate was used as filler with the sufficient quantity to complete the tablet weight to 250 mg.

Tablets preparation procedure

For every formula, the API, binder, dibasic calcium phosphate, sodium starch glycolate and povidone were mixed well for 5 minutes. Then colloidal silicon dioxide and magnesium stearate were added to the powder blend and mixed slowly for 1 minute. Powder blend was then passed through sieve no. 35 then compressed using a rotary tablet compression machine (ZP7 rotary press, Shanghai Yali, China), using size 8.6 mm round bi-concave punch.

2.4 Evaluation of Powder Blends[15-18]

2.4.1 Bulk density

Apparent bulk density (ρb) was determined by placing pre-sieved drug excipients blend into a graduated cylinder and measuring the volume (Vb) and weight (M) as it is.

ρb = M/Vb.

2.4.2 Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed number of taps. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (ρt) was calculated using following formula.

ρt = M/ Vt.

2.4.3 Compressibility index

The simplest way of measurement of free flow property of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by % compressibility which is calculated as follows:

C = (ρt – ρb) / ρt * 100.

ρt:Tapped density, ρb: Untapped bulk density.

2.4.4 Hausner's ratio

Hausner's ratio is an index of ease of powder flow; it is calculate by following formula.

Hausner's ratio = ρt\ ρb

ρt: Tapped density, ρb: Untapped bulk density.

Table 2: The powder blends evaluation.

Parameters	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Bulk density (g/cm3)	0.568	0.47	0.578	0.641	0.521	0.581	0.445	0.61	0.581
Tapped density (g/cm3)	0.781	0.706	0.799	0.862	0.758	0.862	0.623	0.926	0.806
% Compressibility	27.27	33.33	27.58	25.64	31.25	32.56	28.57	34.15	27.91
Hausner's ratio	1.375	1.5	1.381	1.345	1.455	1.483	1.4	1.519	1.387

2.5 Qualification of Tablets

Randomly selected tablets samples from all formulation runs were subjected to different pharmacopoeial tests in order to determine and evaluate their pharmaceutical properties.

2.5.1 Tablets weight variation[19]

Randomly selected 20 tablets of each run were weighed, mean value and relative standard deviations (% RSD) from the mean value for all tablets were calculated and compared to the allowed pharmacopoeial limitations for weight variation.

2.5.2 Tablets friability[19]

For each run, an amount of tablets equivalent to 6.5 g were weighed and tested using digital friability test apparatus (Electronic India, India) rotating at speed of 25 rounds per minute for 4 minutes. Tablets were then de-dusted, re-weighed and friability was calculated as a percentage ratio of the loss in weight to the total weight of tablets before test conduction.

2.5.3 Tablets hardness[19]

10 randomly selected tablets from each formulation run were individually investigated for the force (in kp) required to break the tablets using hardness tester (Copley, Nottingham, UK).

2.5.4 Tablets disintegration time[19]

Six randomly selected tablets were put in the disintegration test apparatus (Electronic India, India), the minimum and maximum time of the tablets to disintegrate was recorded, then the average was calculated.

2.5.5 In vitro drug release test[20]

The dissolution test was carried out using USP paddle apparatus (Electronic India, India) set at 50 rpm. Dissolution medium was 900 ml of phosphate buffer pH 6.8maintained at 37 ± 0.5ºC. For each formulation run 2 tablets were subjected to the test which was conducted for 60 mins and 10ml dissolution samples were withdrawn at intervals of 15 mins, filtered and assayed for the drug spectrophotometrically at λmax273nm (UV-vis spectrophotometer, Shimadzu®, Japan) against phosphate buffer as a blank. The mean cumulative percentage of drug released was calculated and plotted against respective time interval to generate drug release profiles of different runs. For comparative purposes, similarity factor (f2) was calculated using the following equation:[14]

$$f2 = 50 \cdot \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

Where *n* is the number of time points, *Rt* and *Tt* are the dissolution value of the reference and test product at time *t*, respectively.

3. RESULTS AND DISCUSSION

The layout and pharmaceutical attributes of different experimental runs are enclosed in Table 3.

Table 3: Experimental runs layout for the 32 fractional factorial design.

Run	Type of binder	Binder level	Hardness (Kp)	Friability (%)	Disintegration time (min)	Similarity factor (f2%)	Weight variation (RSD%)
1	PGS	15%	6.02	0.29	8.65	67	3.19
2	Maize starch	35%	12.43	0.2	3.44	64	2.76
3	MCC	55%	16.64	0.13	6.41	47	1.74
4	MCC	15%	6	0.34	0.51	45	2.28
5	PGS	35%	4.06	0.66	28.25	38	1.15
6	Maize starch	55%	6.47	0.33	4.86	50	1.96
7	MCC	35%	7.97	0.33	0.55	48	2.11
8	PGS	55%	9.81	0.004	85	17	2.27
9	Maize starch	15%	5.41	0.47	3.86	57	2.54

3.1. Weight variation

Displayed average weights of tablets among different formulations vary insignificantly around the theoretical tablet weight with % RSD ranged between 1.15-3.19% (Table 3). All formulas appear within the accepted requirement for weight variation according to the category of <500 mg solid oral dosage form which requires maximum %RSD of 5% to fulfill the weight variation specifications.[19] Both binder type and concentration appears to affect weight variation considerably.

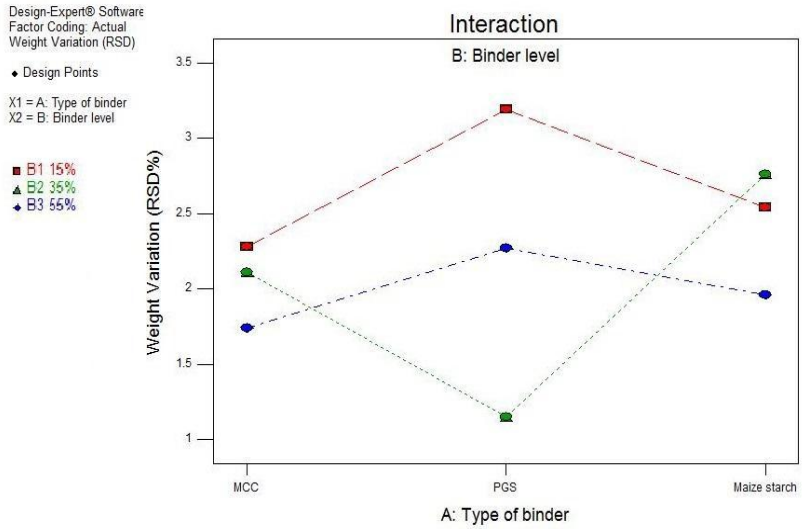

Fig.1: **The weight variation among the nine formulations.**

In general, variation of tablets weight is related mainly to the flowability of the powder blend prior compression, where both binder type and concentration used are expected to affect the formulation flow criteria.

The results reveal that utilization of the lowest concentration of PGS (15%) gives the highest RSD%. While with MCC, it can be seen that as its concentration increases, the RSD% decreases. This might be highly attributed to the good flow properties of MCC.[22] For maize starch the higher concentration yields the lowest RSD%, which might be due to the antiadherent and lubricant effect of maize starch when used in a dry form that led to enhanced powder blend flowability.[21]

3.2. Hardness and friability

For MCC, the increase in hardness as increasing concentration is showing the efficacy of the effect of MCC as a binder.[21] There is a high correlation between hardness and friability as shown in fig. 2, which indicates that the friability decreases as hardness increases, for all the formulas.

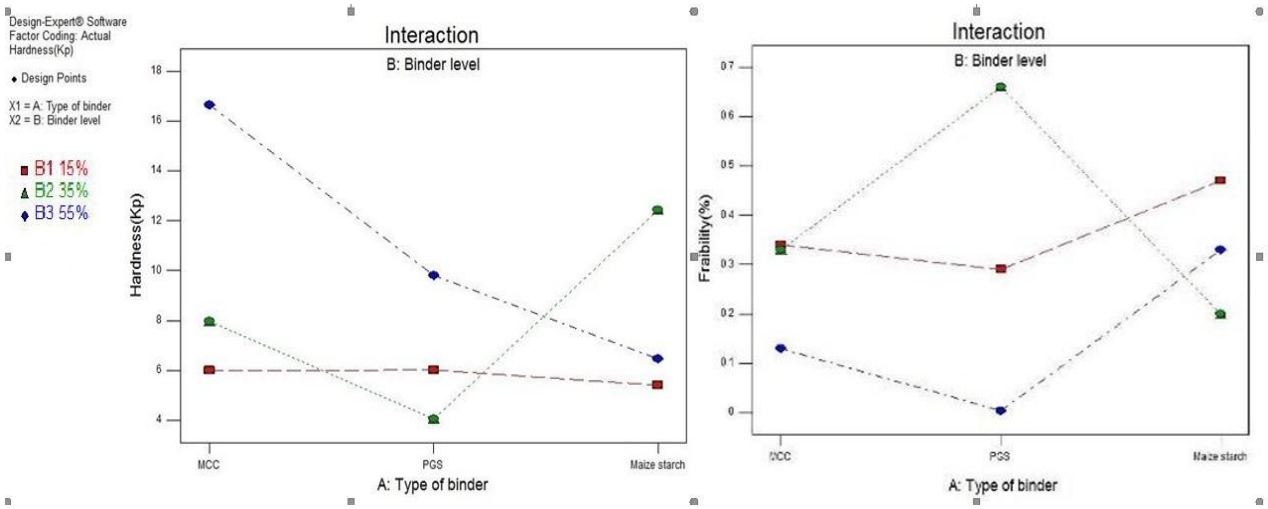

Fig. 2 (a) **Fig. 2 (b)**

Fig. 2: (a) The hardness and (b) the friability and their correlation for the nine formulations.

For maize starch, the lowest concentration obtained the least hardness (highest friability) due to the lack of maize starch binding effect. Starch that is not pregelatinized does not compress well and tends to increase tablet friability and capping if used in high concentrations,[21] which explains the increase in friability when maize starch is used in the high concentration. For that, using PGS with the highest concentration gave the best hardness and friability.

3.3. Disintegration time

For PGS, it can be seen obviously that as its concentration increases the disintegration time decreases significantly (p value = 0.0277).

For MCC, the result indicated that increased hardness value showed increased disintegration time.[22, 23] With the highest concentration, maize starch showed a reduced disintegration time with respect to MCC. This is probably due to the more hydrophilic nature of maize starch[24] compared to the insoluble MCC.[25]

A good swelling ability of maize starch may have an effect to promote faster disintegration with regard to the poor swelling tendency of MCC.[24]

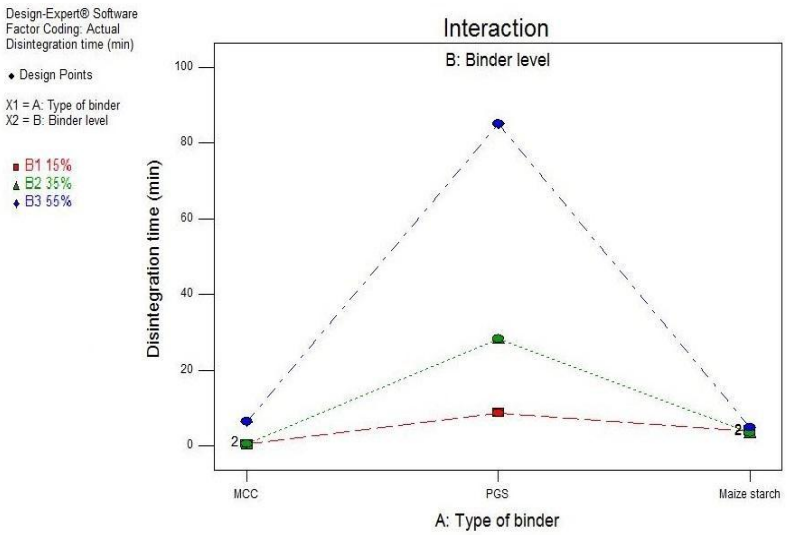

Fig. 3: The disintegration time of the nine formulations.

3.4.Drug release and similarity factor (f2)

The nine formulations showed different dissolution profiles (Fig. 4), which were further compared to the dissolution profile of Cataflam® and the similarity factors (f2) were measured and compared(Fig. 5).As shown in table 3, F1 was found to give the best similarity (67%), closely followed by F2 (64%).

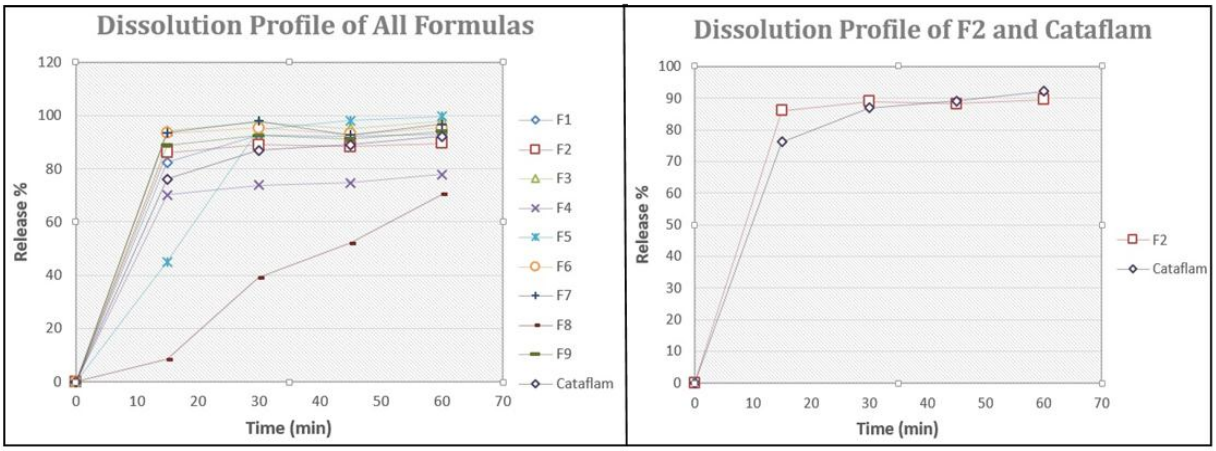

Fig. 4 (a) **Fig. 4 (b)**

Fig. 4: (a) The dissolution profile of the nine formulations and (b) a separated comparison between the two dissolution profiles of F2 and Cataflam®.

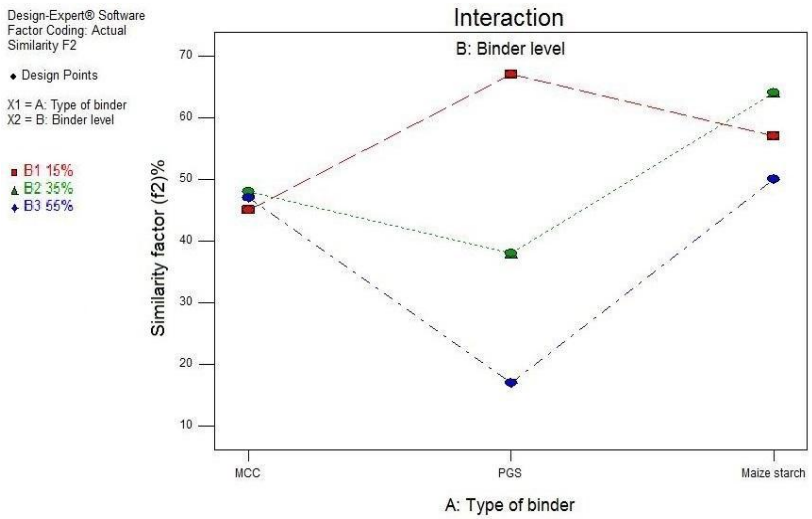

Fig. 5: The similarity factor (f2) of the nine formulations.

4. CONCLUSION

1- Difference in the binder type and level confirmed to influence the weight variation, hardness, friability and specially disintegration time and drug release.

2- PGS was found to have extreme differences in all the tested properties among its different 3 levels.

3- Although F2 (maize starch 35%) obtained the second best similarity factor, it obtained the best friability, hardness, disintegration and weight uniformity than F1 (PGS 15%) that obtained the best similarity. So F2 was chosen as the best formula of the nine formulas.

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