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RESEARCH ARTICLE

Study of Excipients Affecting Dissolution Profile of Drug with Special Emphasis on Co Processed Excipients

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ABSTRACT

The main aim of present work is to study the impact of various excipients and co-processed excipients on dissolution rate. Direct compression is the preferred method for the preparation of tablets. Co processing is the one of the most widely explored and commercially utilized method for the preparation of directly compressible vehicle. The objective of present study is to prepare and characterize various co processed excipients and its application in tablet formulation. Co-processed excipient prepared was characterized by flow properties, solubility, Hardness, Friability, % drug content in tablet formulation. FTIR and SEM show no physical interaction between them with no chemical change. Co processing of excipients was evaluated for Drug release, mean dissolution time and dissolution efficiency Sucrose: MCC (2:1) used to extend the drug release up to 6 hr, we can prepare sustain release tablet of this CO processing by incorporation of sustain release polymer. MCC: Kyron was used to prepare immediate drug release. So based on these properties we was prepared immediate release formulation and sustain release formulation. Co-processing of Sucrose: MCC have been used to achieve sustain release by incorporation of pectin, by using this combination we can achieve sustain release up to 10 hr similarly Kyron: MCC was used in immediate release formulation. Comparison with both IR and SR marketed product and evaluated for F2 test shows there is similarity in dissolution profile between both the batches.

KEYWORDS

Aceclofenac, Co processing, MCC: Kyron, Sucrose: MCC, Excipients.

INTRODUCTION

The present study investigates the preparation of various Co processed excipients and its effect on dissolution rate. Co processing is a mixture of two or more material by an appropriate process, Co processing of excipients may lead to formation of new excipients with added value. The new excipients so formed did not loose their Physical structure and chemical stability.

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Aceclofenac is NSAID, belongs to BCS class II drug, which having poor solubility and bioavailability. In our study excipients and co processed excipients is current focus of research. Excipients play a vital role in Pharma industry, R&D of new drug molecule requires input of huge money and time, and hence research focus is shifting from API to excipients. Co processed excipients especially. The rationale behind this study is to explore the impact of common excipients and co processed excipients on dissolution profile of BCS class II drug. Co processing of excipients was evaluated for Drug release, mean dissolution time and

dissolution efficiency Sucrose: MCC (2:1) used to extend the drug release, we can prepare sustain release tablet of this CO processing by incorporation of sustain release polymer. Similarly MCC: Kyron was used to prepare immediate drug release[1,2]. So based on these properties we was prepared immediate release formulation and sustain release formulation[3,4].

MATERIALS AND METHODS

Aceclofenac was obtained from Aventis Pharmaceutical Ltd, Ahmadabad as a gift sample. Sucrose was obtained from Chemdyes Corporation. MCC, Magnesium stearate and Cross povidone were purchased. Kyron T-314 was obtained from Sun Pharmaceutical, Vapi as a gift sample. Ethanol, Acetone, and Distilled water used as a solvent were purchased.

Method of Preparation of Co-processed Excipients

Co processing was done by solvent evaporation method using various solvent such as water, methanol, acetone and mixture of solvents. According to solubility of excipients. All Ingredients were weighed, put them into petridish. Dissolved them into organic Solvents (mix both Solvents), Solvents were evaporated, Solid mass was obtained then cool it. Put them into Hot Air Oven for drying[5].

Method of Preparation of Tablets from Co-processed Excipients by Direct Compression

Tablets were prepared by direct compression technique. All ingredients were weighed and powdered. Pass them through the 100# sieve. Then separately mixed them into two different mortar Pestle. Then powdered are weighted in tablets weight and punch in tablet punching machine compressed tablets were then evaluated for the various evaluation parameters.

In our study we have prepared co processing of Sucrose: MCC (1:2), to find out the suitable relationship of sucrose and MCC on dissolution profile of BCS class II drug.

Sucrose: Mg stearate, MCC: Mg stearate (100:2) to Study the effect of Mg stearate on dissolution rate.

Superdisintigrant cross povidone: Kyron T-314(1:1)[7,8]

Cross povidone: Mg stearate and Kyron: Mg stearate (5:2)[6]

MCC: Kyron and MCC: Cross povidone (100:5)

During our study we have to prepare various combination of co processing as discussed earlier and find out suitable relationship on dissolution rate.

So from that we find that sucrose: MCC Co processing was used to extend the drug release similar Kyron T-314: MCC was used as immediate release formulation[8].

Based on this we have to prepare immediate release batches shown in Table 1 and sustained release batches shown in Table 2.

Evaluation Parameters

Pre-Compression Studies

The powder blend of formulation batches of API were evaluated for Angle of repose, Bulk density, Tapped density, Carr's index and Hauser's ratio[9,10].

Post-Compression Studies

Weight Variation Test

To study weight variation twenty tablets of the formulation were weighed using a Prompt SPM 300 electronic balance and the test was performed according to the official method[12].

Hardness

The hardness of five tablets was determined using the Dr. Schleunizer type hardness tester and the average values were calculated[13,16].

Friability

The friability was measured by Roche friabilator for 4min at 25rpm for 100 revolutions. Accurately weigh twenty tablets placed into Roche friabilator for 100 revolutions than dedust the tablets and weigh[14,15].

$$\% \text{ Friability} = (W0 - W) * 100 / W0$$

Formulation Batches of Immediate Release Tablets

Table 1: Formulation table for immediate release tablets

Ingredients	F1	F2	F3	F4	F5	F6
Aceclofenac	100	100	100	**100**	100	100
Sucrose	-	-	-	-	-	-
MCC	-	200	-	-	200	-
Sucrose +MCC(2:1)	-	-	-	-	-	-
Lubricant (2%)	-	2mg	2mg	**2mg**	-	-
Sucrose +Lubricant(100:2)	-	-	-	-	-	-
MCC +Lubricant(100:2)	204	-	-	-	-	204
Kyron	5mg					
Kyron +Cross povidone(1:1)	-	5mg	-	-	-	-
MCC :Kyron(100:5)	-	-	-	**210**	-	-
MCC: Cross povidone (100:5)	-	-	210	-	-	-
Cross povidone +Magnesium stearate(5:2)	-	-	-	-	7mg	7mg
Total weight	**309**	**307**	**312**	**312**	**307**	**311**

(All ingredients were in mg)

Formulation Batches for Sustain Release Tablets

Table 2: Formulation table for sustained release tablets

Ingredients	F7	F8	F9	F10	F11	F12	F13	F14
Aceclofenac	**100**	**100**	100	**100**	100	100	100	**100**
Sucrose	-	-	200	-	-	-	-	-
MCC	-	-	-	-	-	-	-	-
Sucrose +MCC(2:1)	**200**		-	**100**	100	100	100	**100**
Lubricant (2%)	**2**		-	-	-	-	-	-
Sucrose +Lubricant(100:2)	-	**204**	-	**102**	-	102	102	**102**
MCC+ Lubricant (100:2)	-	-	-	-	102	-	-	-
Kyron + Cross povidone(1:1)	-	-	-	-	-	-	-	-
MCC :Kyron(100:5)	-	-	-	-	-	-	-	-
MCC:CP(100:5)	-	-	-	-	-	-	-	-
Cross povidone +Magnesium stearate(5:2)	-	-	7	-	-	-	-	-
Pectin	-	-	-	-	-	50	100	**150**
Total weight	**302**	**304**	**307**	**302**	**302**	**352**	**402**	**452**

(All ingredients were in mg)

Swelling Index

Tablets of each formulation were weighed individually (W1) and placed separately in Petri-dishes containing 2% Agar gel. At regular intervals (1, 2, 3, 4, 5, 6, 7 and 8 hours) the tablets were removed from Petri dishes and excess water removed carefully using filter paper. The swollen tablets were re-weighed (W2). The % swelling was calculated from the initial and final weight[17,18].

***In–vitro* Release Study[19]**

Dissolution Parameter

Medium: Phosphate buffer pH 7.4
Volume: 900ml
Apparatus: USP – type II
RPM: 50 rpm
Temperature: 37°C ± 0.5°C

Comparison with Marketed Product

Calculation of f2 Value (Similarity Factor)

This is done for comparing the optimized formulation with marketed formulation. The similarity factor (f_2) was defined by CDER, FDA and EMEA as the "logarithmic reciprocal square root transformation of one plus the mean squared difference in percent dissolved between the test and the reference products". Moore and Flanner give the model independent mathematical approach for calculating a similarity factor *f2* for comparison between dissolution profiles of different samples. The similarity factor (F_2) given by SUPAC guidelines for modified release dosage form was used as a basis to compare dissolution profile[19]. The dissolution profiles of products were compared using F_2. The similarity factor is calculated by following formula,

$$F2=50*\log [\{1+1/n\sum (Rt-Tt)^2 \}^{-0.5}*100] \ldots..(1)$$

Where, n is the number of dissolution time points

R_t – The reference profile at the time point t

Tt - The test profile at the same point.

Table 3: Similarity factor value and its significance

Similarity factor (F2)	Significance
< 50	Test and reference profiles are dissimilar
50 – 100	Test and reference release profiles are similar
100	Test and reference release profiles are identical
> 100	The equation yields a negative value

A value of 100% for the similarity factor suggests that the test and reference profiles are identical. Values between 50 and 100 indicate that the dissolution profiles are similar whilst smaller values imply an increase in dissimilarity between release profiles.

Stability Studies of Optimized Tablets

The ICH Guidelines have established that long term stability testing should be done at 25°C±2°C / 60%±5% RH; stress testing should be done at 40°C±2°C / 75%±5% RH for 6 months. If significant change occurs at these stress conditions, then the formulation should be tested at an intermediate condition at 30°C±2°C /75%±5% RH. Table 6.7 shows different temperatures and period of stability testing[8,13].

Table 4: ICH guidelines for stability study

Study	Storage condition	Minimum time period covered
Long term	25°C±2°C / 60%±5%	12 Months
Intermediate	30°C±2°C / 65%±5%	6months
Accelerated	40°C±2°C / 75%±5%	6 months

The stability studies of the optimized tablets were carried out at 40○C temperature and 75 % relative humidity (accelerated stability) in stability chamber for three months.

RESULTS AND DISCUSION

FTIR Spectrum of alone Aceclofenac and different Co processed excipients showed not any type of compatibility and physical interaction after Co precipitation. Results are shown in Figure 1 to Figure 5. F1 to F14 batches of tablets were prepared by Co precipitation method and Evaluation parameters like Disintegration time, Friability, Hardness, mean dissolution time, % drug entrapment were carried out. From that F1 to F6 batches of tablets showed immediate release and F4 batch showed 6.23 sec. Disintegration time while F7 to F14 batches of tablets Showed Sustained release and F14 batch showed sustained release upto 10 hrs. Results are shown in Table 5 and Figure 6 to Figure 8. F12, F13 and F14 batches showed % Swelling Index 21.12, 26.3 and 38.1 respectively. Results are shown in Table 5. Scanning electron microscopy of Co processing MCC: Sucrose show absorption of sucrose on surface of MCC due to hydrophilic nature of sucrose. Results are shown in Figure 9. Scanning electron microscopy shows Co processing of Kyron: MCC having faster disintegration rate than other formulation. Results are shown in Figure 10. Magnesium stearate was hydrophobic in nature, so SEM shows hydrophobic layer around MCC surface and retard drug dissolution. Results are shown in Figure 11.

Table 5: Evaluation parameters for optimized batches of Co processed Excipients

Study	DT	Hardness gm/cm3	Friability (%)	MDT(min)	DE (%)
F1	17.82 sec	4.3±1.1	0.36	21.67	66.84
F2	24.32 sec	4.5±1.5	0.68	24.91	58.04
F3	11.88 sec	3.9±1.1	0.31	17.06	81.09
F4	**06.23 sec**	**4.4±1.7**	**0.34**	**21.70**	**85.92**
F5	13.83 sec	3.6±2.5	0.54	20.66	68.97
F6	12.75 sec	3.8±1.5	0.37	21.68	66.62
F7	38.05min	4.1±0.9	0.47	2.76(hr)	49.93
F8	20.16min	3.9±2.3	0.68	2.34(hr)	56.04
F9	1.02 min	3.7±1.9	0.36	27.52	54.46
F10	52.10min	4.7±1.4	0.47	3.07(hr)	53.09
F11	8.53 min	**4.2±2.4**	0.26	38.61	62.36
F12	-	7.3±1.6	0.16	4.82(hrs)	37.28
F13	-	6.8±1.8	0.27	4.19(hrs)	41.70
F14	**-**	**7.4±2.1**	**0.37**	**4.89(hrs)**	**47.30**

Table 6: Swelling Index of F12, F13 and F14 batches.

Batch	Swelling index (%) 1 hr
F12	21.12±1.2
F13	26.3±0.9
F14	38.1±1.4

(All values are expressed as mean ± S.D n=3.)

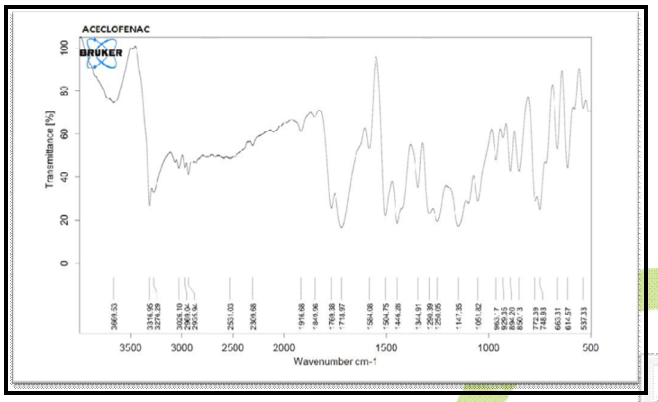

Figure 1: FTIR Spectrum of Aceclofenac

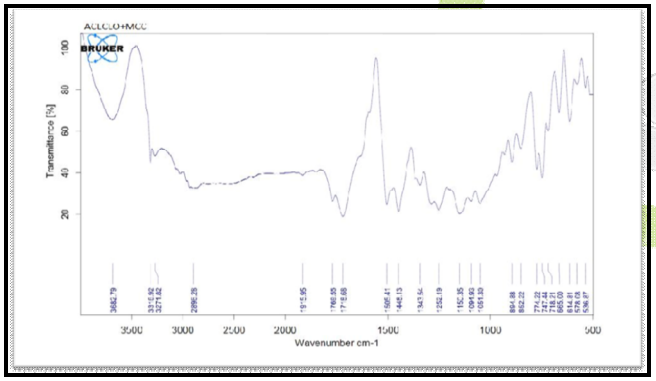

Figure 2: FTIR Spectrum of Aceclofenac and MCC

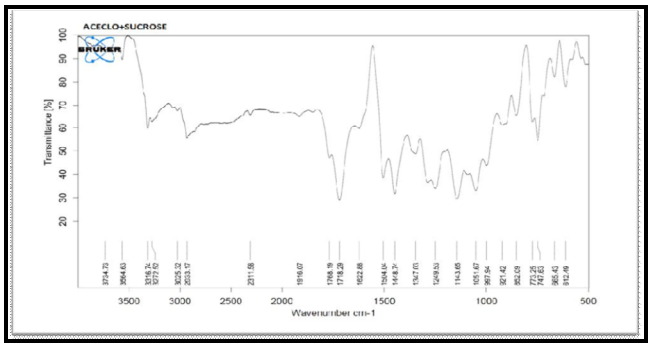

Figure 3: FTIR Spectrum of Aceclofenac + Sucrose

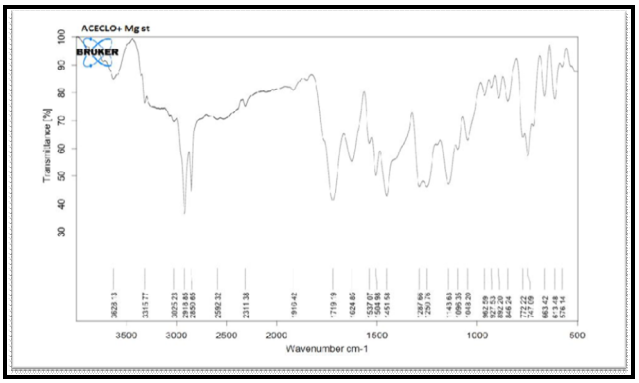

Figure 4: FTIR Spectrum of Aceclofenac + Magnesium Stearate

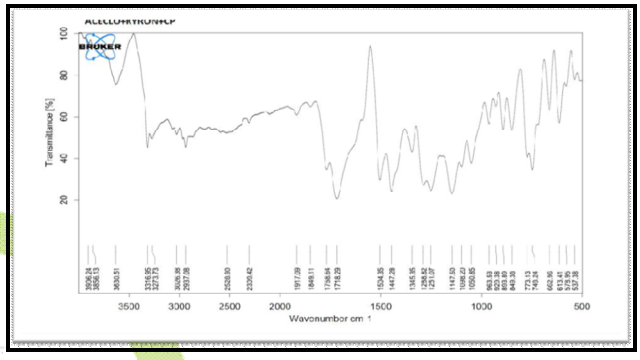

Figure 5: FTIR Spectrum of *Aceclofenac+ Kyron + Cross-povidon*

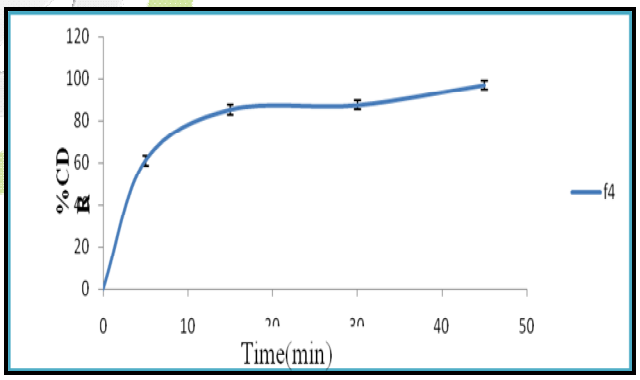

Figure 6: %CDR of immediate release batch F4.

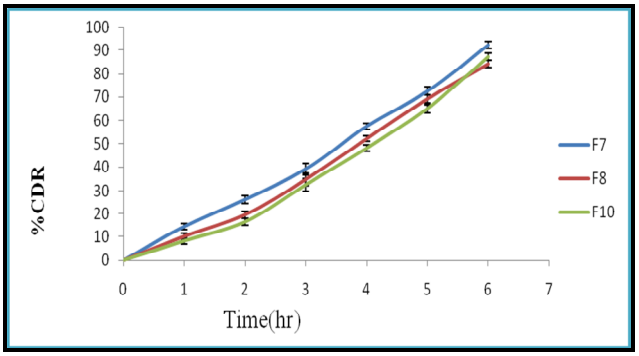

Figure 7: %CDR of F7, F8 and F10 batches.

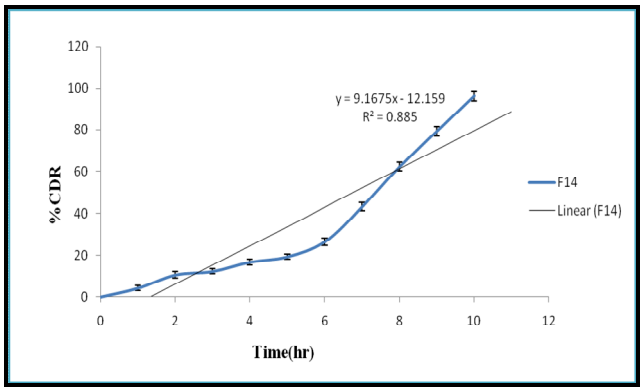

Figure 8: %CDR of release sustained release batch F14.

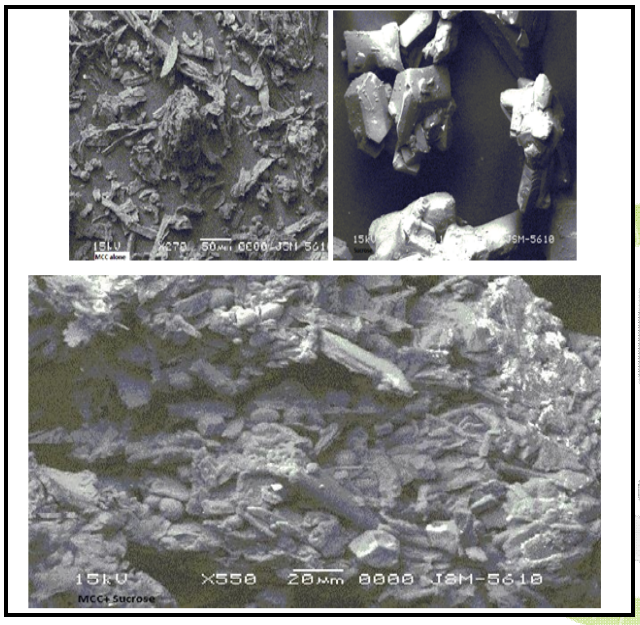

Figure 9: SEM of Co processed MCC + Sucrose

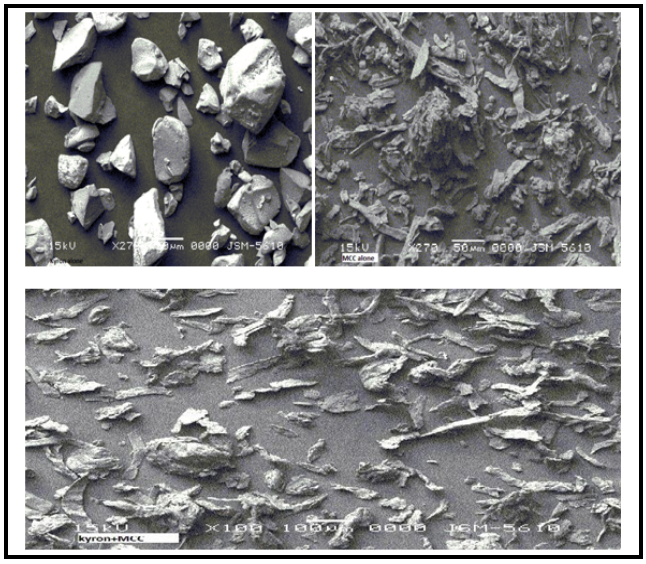

Figure 10: SEM of Co processed Kyron +MCC

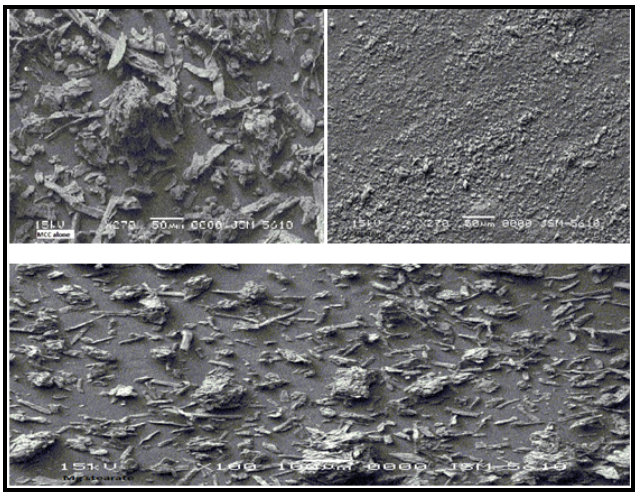

Figure 11: SEM of Co processed MCC + Mg stearate

CONCLUSION

Co processed of excipients prepared by co precipitation method show good powder characteristic, FTIR, SEM confirmed the physical interaction between the two components with no chemical interaction take place. Batch F4 show immediate release while batch F6, F7 and F10 show sustained release action. We were further incorporate batch F10 with sustain release polymer (batch F14) that show sustain release with respect to direct compressible tablet formulation.

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