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FORMULATION OF DIRECT COMPRESSED VERAMPAMIL SUSTAINED RELEASE FORMULATION USING OPTIMIZED CO PROCESSED EXCIPIENTS

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Keywords:

Co processed, HPMC, Microcrystalline cellulose, Stearic Acid, Cetostearyl Alcohol, Guar Gum and Maize Starch

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ABSTRACT: Pharmaceutical excipients when co-processed have improved flow and disintegrant properties in tablet formulations. However, physical mixtures of excipients show limited functions, poor flow properties, and poor functional properties so they cannot be used directly in tablet formulations. Majority of solid dosage forms contain multiple excipients, which provides a wide window of opportunities by combining existing excipients to achieve the desired set of performance characteristics. Over the years, the development of single-bodied excipient combinations at a sub-particle level, called co-processed excipients which deals with particle engineering, has gained huge importance. Co-processing involves interaction of two or more excipients at the sub-particle level aimed at providing a synergy of functionality improvements, as well as masking the undesirable properties of the individual excipients. Preparation of co-processed excipients involves incorporation of one excipient into the particle structure of another, using Co-Drying and Melt granulation technology. Co-processing is primarily aimed at addressing the issues of flow ability, compressibility and disintegration potential. Co-processing of excipients is multifaceted with the characteristic properties like Absence of chemical change, Improved Flow Properties, Improved Compressibility, Better dilution potential, reduced lubricant sensitivity and multiple advantages like reducing inventory burden, reduced product cost etc.

INTRODUCTION: Co-processed excipients by virtue of combining properties of two different excipients fulfill the increasing demand of multifunctional excipients for direct compression tabletting. Co-processed excipients are prepared by incorporating one excipient into the particle structure of another excipient using processes such as co-drying. The co-processed multi-component-based excipients are introduced to achieve better characteristics and tabletting properties than a single substance or the physical mixtures [1-5].

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They have been developed primarily to address the issues of flowability, compressibility, and disintegration potential.

Co-processed excipients are appropriate for consideration as new monographs because one or more of the components may be formed in-situ, or the component may not be isolated prior to co-processing. That is, the manufacturing process for one component may not have been taken to completion before the addition of the other components, and/or the co-processed excipient combination cannot be adequately controlled using the monograph tests for the individual component excipients [6].

Co-processed excipients are a mixture of two or more existing excipients at sub particle level, offer substantial benefits of the incorporated excipients

and minimize their drawbacks. These multipurpose excipients have significantly reduced the number of incorporating excipients in the tablet. The present article discusses the development and source of new excipients, potential advantages of co-processed excipients, material characteristics required for coprocessing, methods of preparing directly compressible adjuvants and various co-processed excipients for direct compression available in the market [7].

MATERIALS AND METHODS:

Materials:

Verapamil HClwas obtained as gift samples from EMCO Industries, Hyderabad. Different grades of HPMC (DOW Chemicals, USA), microcrystalline cellulose (FMC Biopolymer), Stearic Acid (Dow Chemicals, USA), Cetostearyl Alcohol (Alpha Chemika, Mumbai), Guar Gum (Hindustan Gum, India), Lactose (DFE Pharma, India), Sugar (Avantor, India)and Maize Starch(Meru Chem, Mumbai) were obtained.

Methods for Co processing of excipients:

Co drying:

Aqueous solution of parent excipient is prepared by dissolving it in selected/suitable liquid/solvent (water). This aqueous solution is transferred to a beaker which is kept on a heating mantle (at 80^0c), after 2-3 minutes add selected excipient (second excipient) to the beaker slowly by stirring continuously. Now this slurry is added to a pre-heated pan and kept in a hot oven (at 80^{0c}c). To avoid formation of gel the pan must be pre-heated and sufficient head should be supplied to evaporate the water/solvent. When the water/solvent is evaporated completely, the dry powder/co-processed product is collected to characterize and evaluate to know its flow properties and functionality.

Melt granulation:

This technique is best suitable for excipients with low melting point. First Stearic acid is taken in petri dish and heated at 80^0c temperature until turns to liquid state; to this Maize starch is added slowly on constant stirring, while stirring the temperature should be maintained at 80^0c constantly. After constant mixing for 5-10minutes, it is cooled and the product we get is a solid wax which is triturated and sieved (no. 60) to get uniform particle size. This co-processed product is collected to characterize and evaluate to know its flow properties and functionality.

Preformulation studies:

The Co processing of selected excipients are done in three ratios 8:2, 6:4 and 4:6. The selected ratio of Co processed excipients were subjected to pre compressions parameters like Bulk density, Tapped density, % Compressibility index, Hausner ratio and Angle of repose.

Drug excipient compatibility studies:

The drug-excipient compatibility studies were done for pure drugs and pure drug and Co processed excipient combinations by FT-IR studies.

Scanning Electron Microscopy (SEM) and Photomicroscopy:

The optimized compositions of co-processed excipient products which posses good characteristics properties as well as suitable for controlled release oral solid dosage forms were done SEM.

X-ray diffraction (XRD):

XRPD profiles were measured using an X-ray diffractometer (PW1729, Philips, Holland). The range and the chart speed were set at 2×10^3 cycles/sec and 10 mm/βθ, respectively.

Calibration curve preparation:

Suitable analytical method was developed for the Verapamil HCl using UV spectrophotometer in pH 6.8 buffer. The λ_{max} of the Verapamil HCl in pH 6.8 buffer was found to be 278 nm.

Preparation of Tablets:

Tablets are prepared with excipients co-processed at optimum ratio by direct compression method. 500mg weight sustained release tablets containing 50mg dose of Verapamil are prepared with all the optimized co-processed excipient products.

Dissolution profile studies:

All formulations were subjected to dissolution profile studies in 0.1N HCl as per the following conditions:

Apparatus **:** USP Type II

Dissolution Medium **:** 900 ml,

RPM **:** 50 rpm

Temperature **:** 37º ± 2ºC

Time points (hrs) **:** 0, 1, 2, 4, 8, 12, and 20

5 ml of sample was withdrawn at each time point, suitably diluted and absorbance was measured at 215 nm. The % drug dissolved was calculated by comparing the absorbance with that of a standard Aripiprazole solution measured at 215 nm. The 5 ml sample withdrawn was replaced with fresh 5 ml 0.1N HCl.

RESULTS AND DISCUSSION:

TABLE 1: CHARACTERIZATION OF CO-PROCESSED PRODUCTS OF DIFFERENT FORMULATIONS AT RATIO 8:2

Formulation	Composition	Bulk density	Tapped density	Hausner's ratio	Carr's index	Angle of repose
F1	MCC + K15M	0.67	0.91	1.36	24.4	35.5
F2	MCC + K100M	0.62	0.92	1.48	32.6	38.5
F3	MCC+ GG	0.67	0.91	1.36	24.4	35.5
F4	MCC + CSA	0.67	0.91	1.36	24.4	35.5
F5	MCC+SA	0.62	0.92	1.48	32.6	38.5
F6	Lactose+K15M	0.67	0.91	1.36	24.4	35.5
F7	Lactose+ K100M	0.62	0.92	1.48	32.6	38.5
F8	Lactose+GG	0.67	0.91	1.36	24.4	35.5
F9	Lactose+CSA	0.67	0.91	1.36	24.4	35.5
F10	Lactose+SA	0.62	0.92	1.48	32.6	38.5
F11	Sugar+K15M	0.67	0.91	1.36	24.4	35.5
F12	Sugar+K100M	0.62	0.92	1.48	32.6	38.5
F13	Sugar+GG	0.62	0.92	1.48	32.6	38.5
F14	Sugar+CSA	0.67	0.91	1.36	24.4	35.5
F15	Sugar+SA	0.62	0.92	1.48	32.6	38.5
F16	Maize Starch + Stearic acid	0.67	0.91	1.36	24.4	35.5

Polymers of different formulations which are co-processed in the ratio **8:2** show poor flow properties (**Table 1**).

TABLE 2: CHARACTERIZATION OF CO-PROCESSED PRODUCTS OF DIFFERENT FORMULATIONS AT RATIO 6:4

Formulation	Composition	Bulk density	Tapped density	Hausner's ratio	Carr's index	Angle of repose
F17	MCC + K15M	0.71	0.83	1.18	14.5	26.2
F18	MCC + K100M	0.71	0.83	1.18	14.5	26.6
F19	MCC+ GG	0.71	0.83	1.18	14.5	26.0
F20	MCC + CSA	0.71	0.83	1.18	14.5	27.3
F21	MCC+SA	0.71	0.83	1.18	14.5	26.1
F22	Lactose+K15M	0.71	0.83	1.18	14.5	27.3
F23	Lactose+ K100M	0.67	0.80	1.17	15.0	26.3
F24	Lactose+GG	0.67	0.80	1.17	15.0	26.3
F25	Lactose+CSA	0.67	0.80	1.17	15.0	26.7
F26	Lactose+SA	0.71	0.83	1.18	14.5	27.3
F27	Sugar+K15M	0.71	0.83	1.18	14.5	26.7
F28	Sugar+K100M	0.71	0.83	1.18	14.5	26.9
F29	Sugar+GG	0.67	0.80	1.17	15.0	26.3
F30	Sugar+CSA	0.67	0.80	1.17	15.0	27.3
F31	Sugar+SA	0.71	0.83	1.18	14.5	26.5
F32	Maize Starch + Stearic acid	0.67	0.80	1.17	15.0	26.3

Excipients of different formulations co-processed at the ratio **6:4** show good flow properties and they are optimized (**Table 2**).

TABLE 3: CHARACTERIZATION OF CO-PROCESSED PRODUCTS OF DIFFERENT FORMULATIONS AT RATIO 4:6

Formulation	Composition	Bulk density	Tapped density	Hausner's ratio	Carr's index	Angle of repose
F33	MCC + K15M	0.67	0.91	1.36	24.4	30.4
F34	MCC + K100M	0.62	0.92	1.48	32.6	35.5
F35	MCC+ GG	0.67	0.91	1.36	24.4	36.7
F36	MCC + CSA	0.62	0.92	1.48	32.6	33.9
F37	MCC+SA	0.62	0.92	1.48	32.6	35.7
F38	Lactose+K15M	0.67	0.91	1.36	24.4	37.9
F39	Lactose+K100M	0.62	0.92	1.48	32.6	38.3
F40	Lactose+GG	0.67	0.91	1.36	24.4	39.4
F41	Lactose+CSA	0.62	0.92	1.48	32.6	31.2
F42	Lactose+SA	0.67	0.91	1.36	24.4	34.6
F43	Sugar+K15M	0.62	0.92	1.48	32.6	38.5
F44	Sugar+K100M	0.67	0.91	1.36	24.4	37.2
F45	Sugar+GG	0.67	0.91	1.36	24.4	35.9
F46	Sugar+CSA	0.62	0.92	1.48	32.6	36.9
F47	Sugar+SA	0.67	0.91	1.36	24.4	39.3
F48	Maize Starch + Stearic acid	0.62	0.92	1.48	32.6	36.9

Polymers of different formulations which are co-processed in the ratio **4:6** show poor flow properties (**Table 3**). Over all, excipients co-processed at **6:4** ratio shows good flow properties, this ratio of composition seems to be better one in which co-processed excipient products show advanced/additional properties which are absent in individual and their physical mixtures & so they are optimized for formulation of tablets.

FT-IR Studies:

FT-IR analysis is done for only these 6 co-processed excipient products,

F23 (Lactose + HPMC K100M)

F24 (Lactose + Guar gum)

F25 (Lactose + CSA)

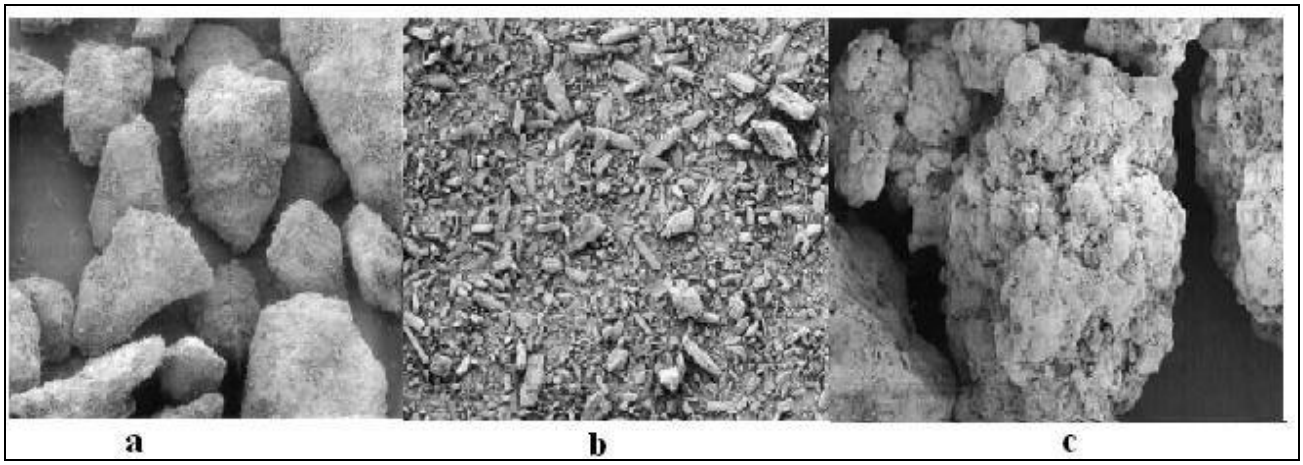
F29 (Sugar + Guar gum)

F30 (Sugar + CSA)

F32 (Maize Starch + Stearic acid)

Scanning Electron Microscopy (SEM) and Photo microscopy:

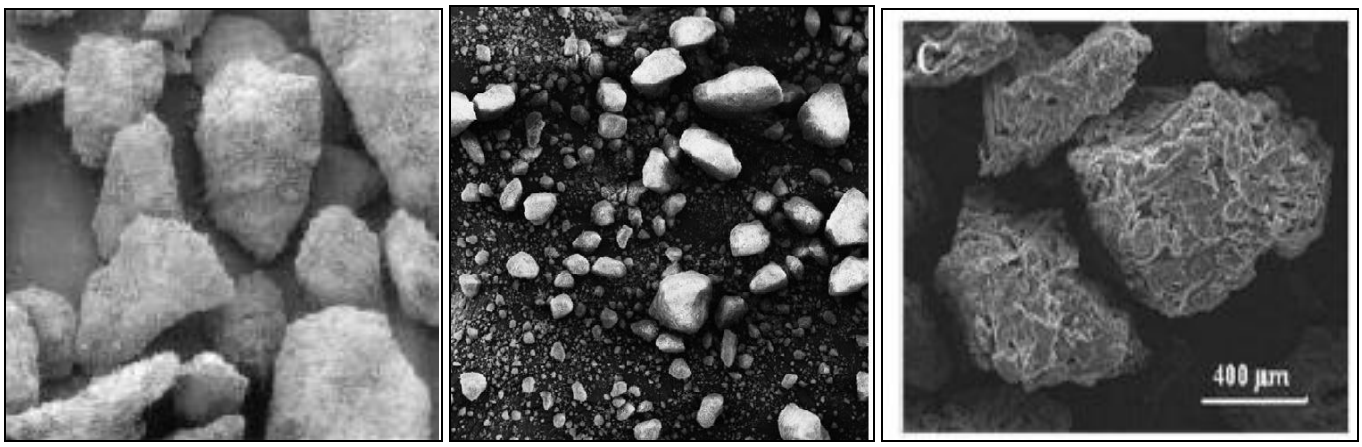
There are 5 optimized compositions of co-processed excipient products which possess good characteristics properties as well as suitable for controlled release oral solid dosage forms.



(a)Lactose **(b) HPMC K100M** **(c) Lactose+HPK100M (Co-processed)**

FIG.1: F23 (LACTOSE + HPMC K100M)

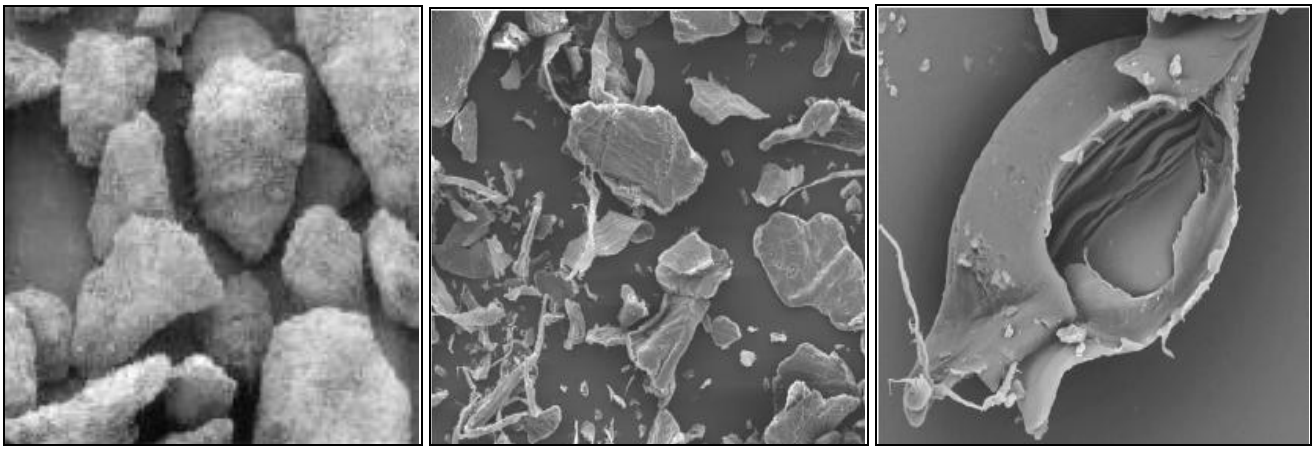
SEM of co-processed excipient product when compared to SEM of individual excipients indicates spherical, porous structures which show good free flowing properties (**Fig. 1**)



(a)Lactose **(b) Guar Gum** **(c) Lactose + Guar Gum co-processed**

FIG.2: F24 (LACTOSE + GUAR GUM)

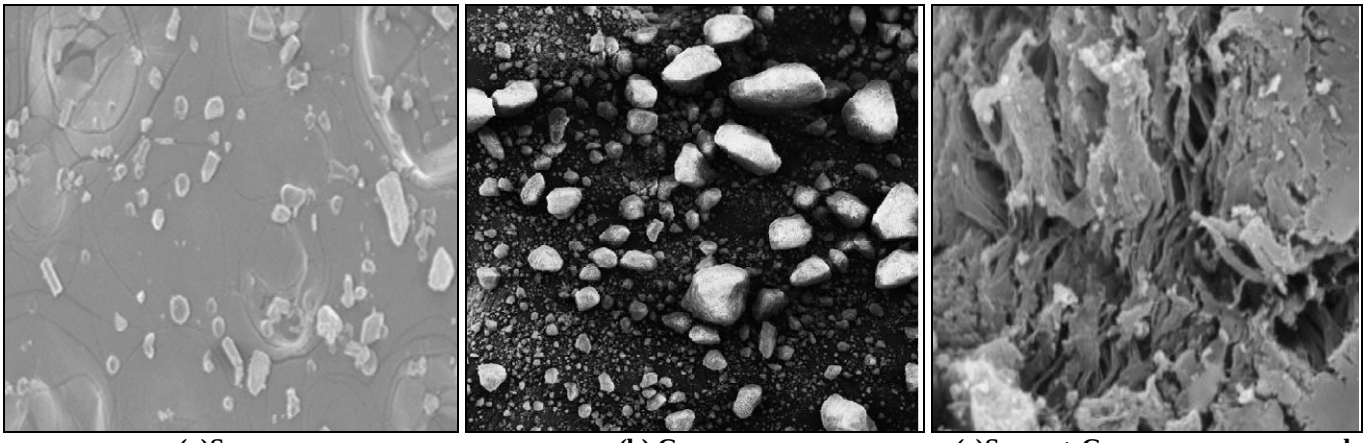
SEM of co-processed excipient product when compared to SEM of individual excipients indicates spherical, porous structures which show good free flowing properties (**Fig. 2**).



(a)Lactose **(b) CSA** **(c) Lactose+CSA co-processed**

FIG.3: F25 (LACTOSE + CSA)

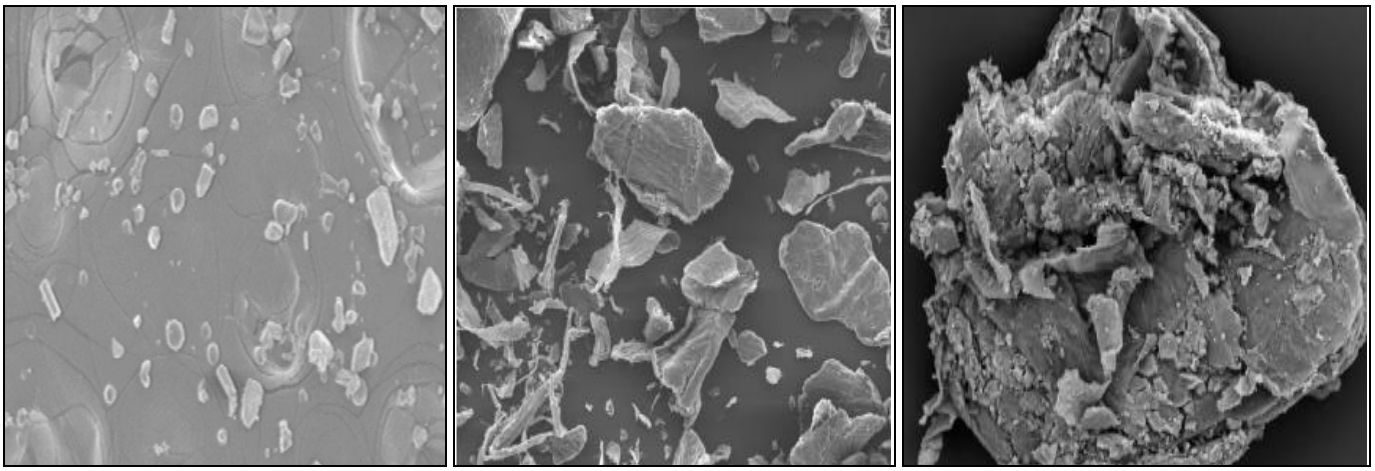
SEM of co-processed excipient product when compared to SEM of individual excipients indicates spherical, porous structures which show good free flowing properties (**Fig. 3**).



(a)Sugar **(b) Guar gum** **(c)Sugar + Guar gum co-processed**

FIG.4: F29 (SUGAR + GUAR GUM)

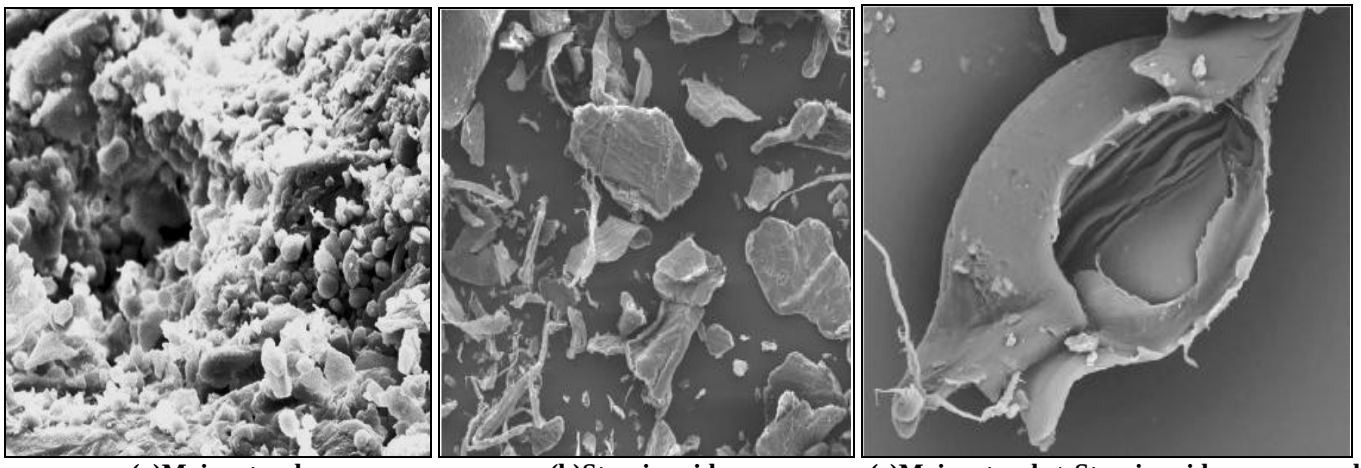
SEM of co-processed excipient product when compared to SEM of individual excipients indicates spherical, porous structures which show good free flowing properties (**Fig. 4).**



(a)Sugar **(b) CSA** **(c) Sugar + CSA co-processed**

FIG.5: F30 (SUGAR + CSA)

SEM of co-processed excipient product when compared to SEM of individual excipients indicates spherical, porous structures which show good free flowing properties (**Fig.5**).



(a)Maize starch **(b)Stearic acid** **(c)Maize starch + Stearic acid co-processed**

FIG. 6: F32 (MAIZE STARCH + STEARIC ACID)

SEM of co-processed excipient product when compared to SEM of individual excipients indicates spherical, porous structures which show good free flowing properties (**Fig. 6).**

Photo-Microscopy:

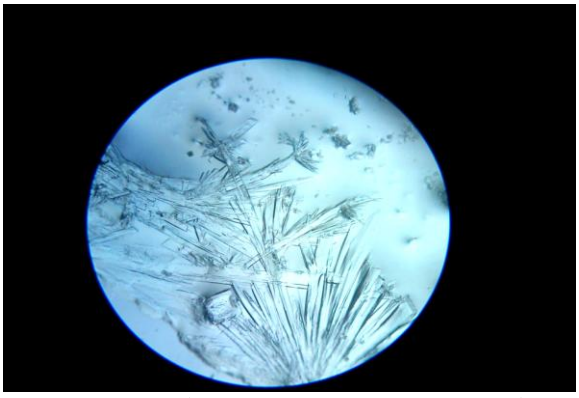


FIG.7: F23 (LACTOSE + HPMC K100M)

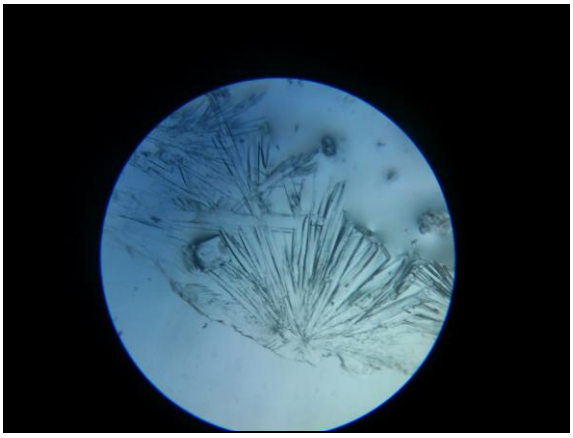


FIG. 8: F24 (LACTOSE + GUAR GUM)

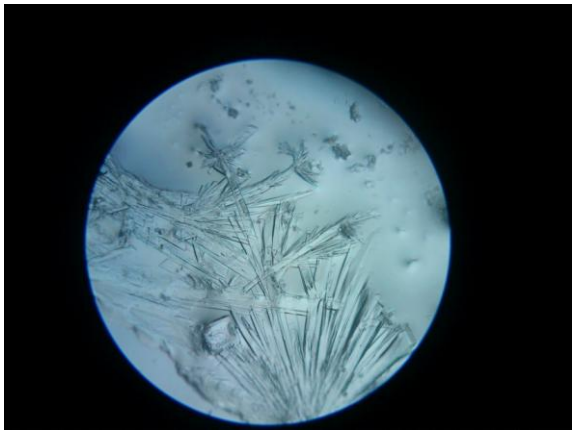


FIG.9: F25 (LACTOSE + CSA):

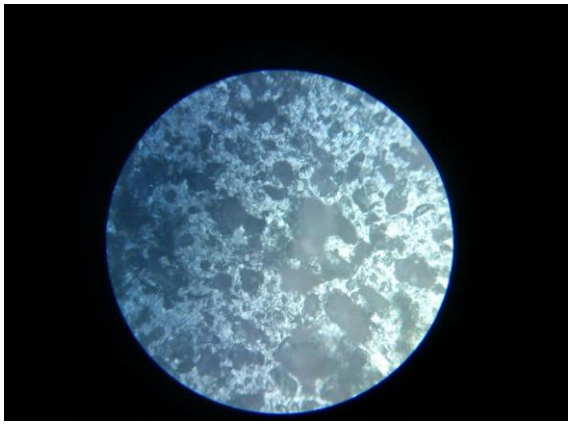


FIG. 10: F29 (SUGAR + GUAR GUM)

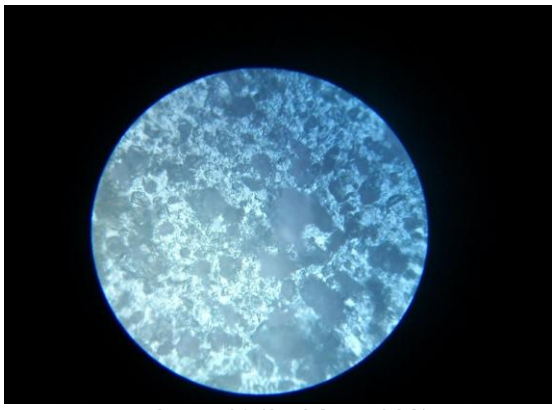


FIG.11: F30 (SUGAR + CSA)

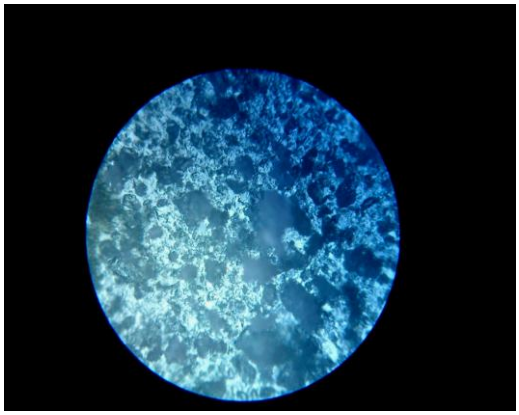


FIG.12: F32 (MAIZE STARCH + STEARIC ACID)

The photomicroscopy of all the co processed excipients are found to be very porous in comparison to individual excipients (**Fig.7** to **Fig. 12**).

X ray diffraction:

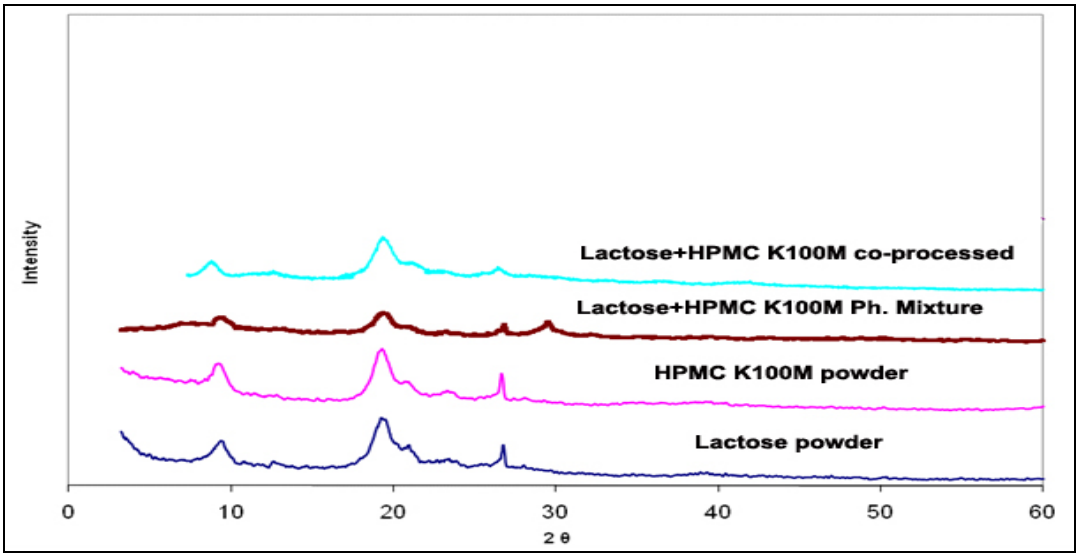


FIG.13: F23 (LACTOSE + HPMC K100M)

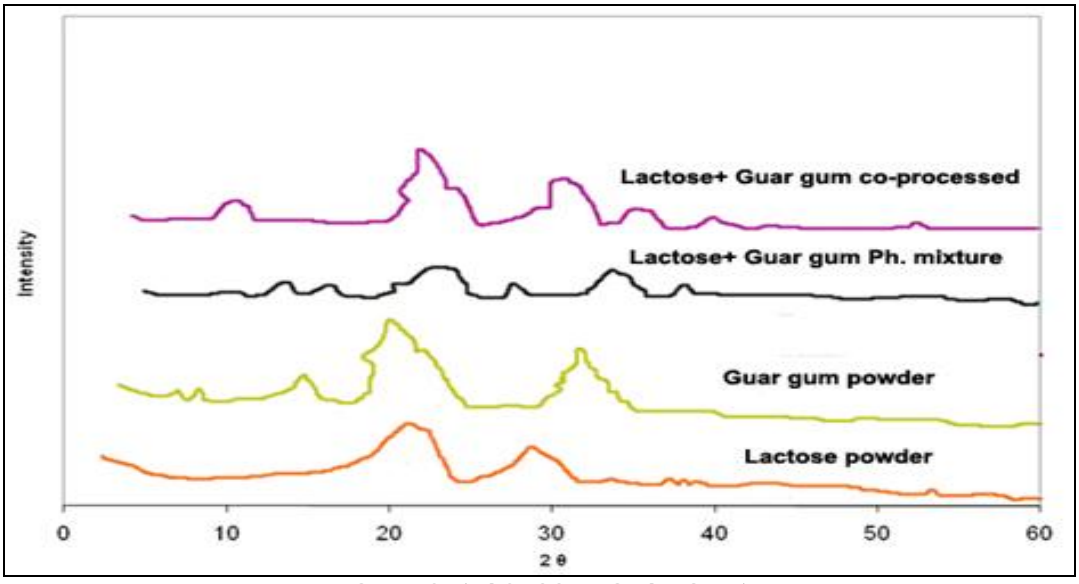


FIG.14: F24 (LACTOSE + GUAR GUM)

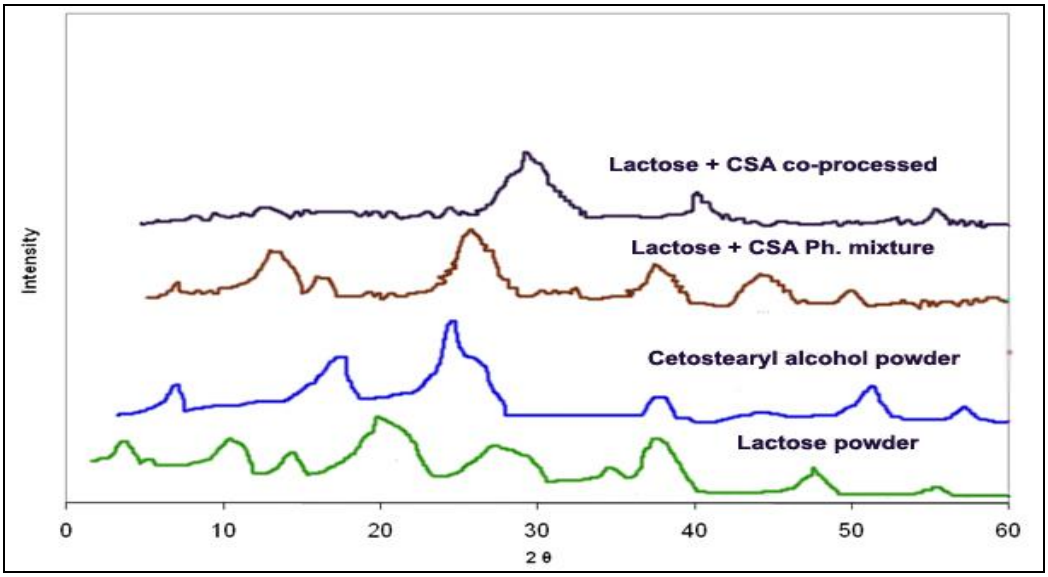


FIG.15: F25 (LACTOSE + CSA)

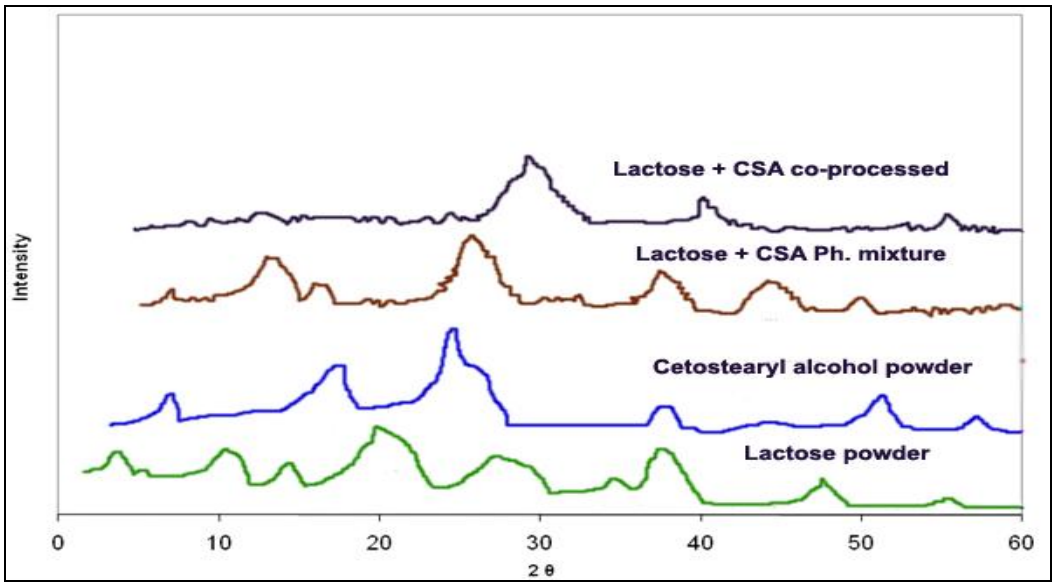


FIG.16: F29 (SUGAR + GUAR GUM)

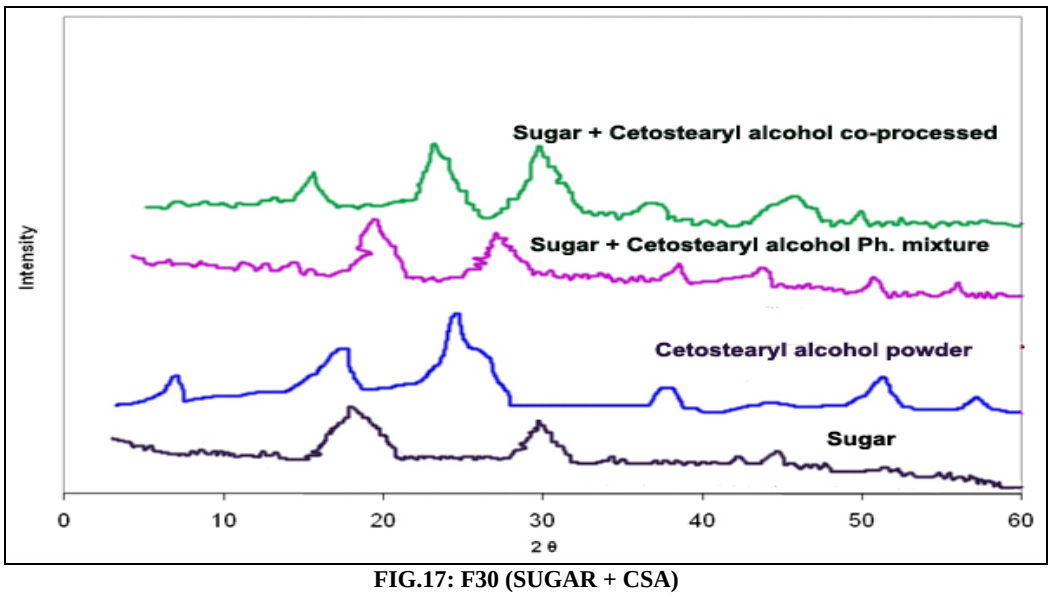


FIG.17: F30 (SUGAR + CSA)

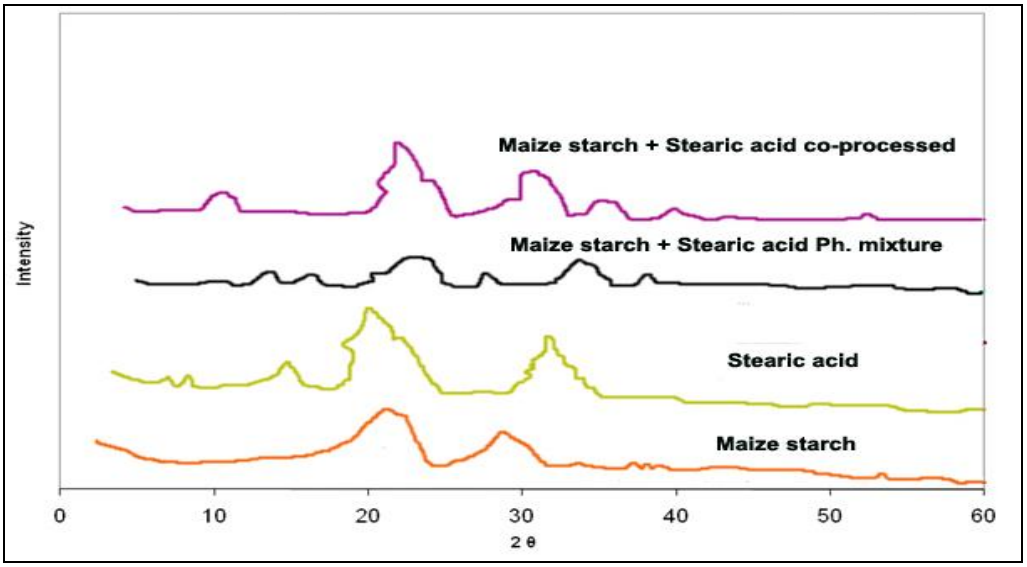


FIG.18: F32 (MAIZE STARCH + STEARIC ACID)

Here, co-processed excipients show broader peaks compared to individual and physical mixture, these broader peaks are indication of number of hydrogen bonds within and between the molecules. Co-processed excipient products exhibit strong binding properties properties when used in pharmaceutical solid dosage forms (**Fig.13-18).**

Calibration curve:

Suitable analytical method was developed for the Verapamil HCl using UV spectrophotometer in pH 6.8 buffer. The λ_{max} of the Verapamil HCl in pH 6.8 buffer was found to be 278 nm. The calibration curve of Verapamil HCl was found to be linear.

Preparation of Tablets:

Tablets are prepared with excipients co-processed at 6:4 ratio only.

Sustained release tablets of Verapamil HCl:

500mg weight tablets containing 50mg dose of Verapamil are prepared with all the five optimized co-processed excipient products (6:4 ratio). These optimized co-processed products have good flow properties and desirable to prepare tablets by direct compression method, a very time saving technique and does not show any problem to high compression forces.

TABLE 4: CHARACTERIZATION OF TABLETS

S.No	Formulation No.	Hardness MN	Thickness Mm	Friability % w/w
1	F22	97.68	6.4	0.122
2	F24	98.06	6.3	0.127
3	F29	98.10	6.5	0.123

All the formulations were within the acceptable range of friability values and possessed good hardness (**Table 4**).

Dissolution profile studies:

All formulations were subjected to dissolution profile studies in 0.1N HCl as per the following conditions:

Apparatus : USP Type II

Dissolution Medium : 900 ml,

RPM : 50 rpm

Temperature : 37º ± 2ºC

Time points (hrs) : 0, 1, 2, 4, 8, 12, and 20

TABLE 5: *IN VITRO* DISSOLUTION DATA PROFILE OF DRUG WITH 0.1 HCL.

Time(hrs)	MCC				
	K15M	K100M	GG	CSA	SA
0	0	0	0	0	0
1	67.56	40.68	56.78	47.78	32.54

2	88.67	68.78	80.97	53.57	43.56
4	100	80.76	95.07	67.12	56.41
8	100.07	89.21	98.99	85.46	65.57
12	100	95.34	99.65	90.89	73.57
24	100	100	100	94.71	91.07

Time(hrs)	**Lactose**				
	K15M	**K100M**	**GG**	**CSA**	**SA**
0	0	0	0	0	0
1	35.78	7.41	6.57	12.07	9.57
2	57.07	13.49	11.34	20.65	13.89
4	75.45	33.08	27.08	30.55	22.68
8	80.99	61.56	67.86	40.98	33.24
12	94.63	83.86	80.09	60.78	58.57
24	100	99.04	97.45	78.76	67.07

Time(hrs)	**Sugar**				
	K15M	**K100M**	**GG**	**CSA**	**SA**
0	0	0	0	0	0
1	30.71	10.67	9.65	8.67	5.17
2	49.077	33.5	10.54	12.34	8.21
4	68.91	45.68	33.43	16.89	10.18
8	77.65	58.27	68.76	20.67	14.3
12	85.99	68.19	84.46	22.54	18.54
24	93.76	73.46	100.09	44.78	34.17

Verapamil HCl tablets prepared with optimized co-processed excipient product (6:4 ratio),

F23 (Lactose + HPMC K100M),

F25 (Lactose + CSA),

F30 (Sugar + CSA)

Show desired dissolution profile of that of a marketed/innovator controlled release tablets (**Table 5** and **Fig. 19**).

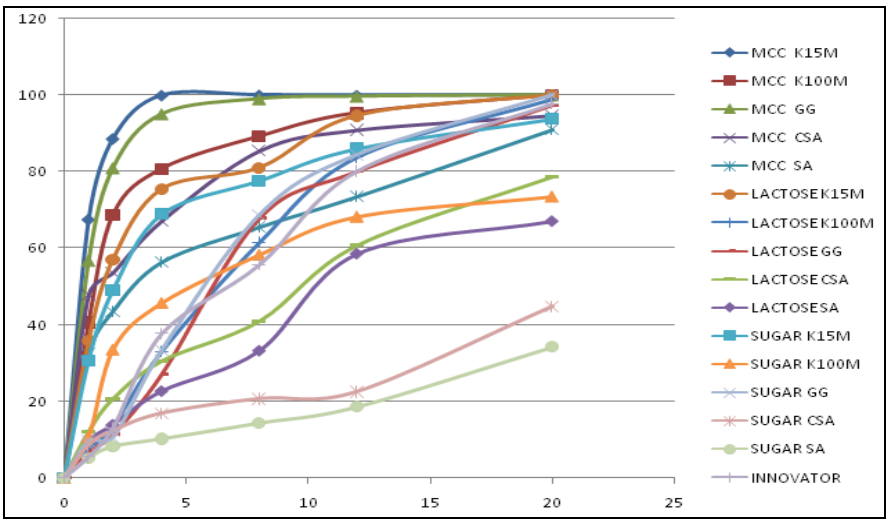


FIGURE 19: *IN VITRO* DISSOLUTION DATA PROFILE

SUMMARY AND CONCLUSION:

Verapamil HCl tablets of compositions F23, F25, and F30 show desired dissolution profile of that of marketed/innovator controlled release tablets. Based on dissolution profile, drug release rate kinetics is determined as follows:

F23 (Lactose + HPMC K100M) is Hixson-Crowell Model dependent.

F25 (Lactose + CSA) is Korsmeyer-Peppas Model dependent.

F30 (Sugar + CSA) is Hixson-Crowell Model dependent.

Here, the Objective of preparing a co-processed excipient product which can be used as a strong binder to prepare controlled release tablets is achieved. Moreover it is added advantage of all co-processed excipients that they possess good flow properties suitable for direct compression technique which reduces production times and costs and there are many more added advantages of direct compression technique.

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