Preparation and *in vitro* evaluation of novel co-processed excipient for formulation of extended-release tablet containing weakly basic drug

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Abstract

The aim of the current study was to prepare a novel co-processed excipient for extended-release tablet dosage form of weakly basic drug**.** The co-processed excipient was prepared from hydroxypropyl methyl cellulose (HPMC) as a hydrophilic polymer and hydrogenated castor oil (HCO) as a hydrophobic ingredient and anhydrous citric acid as an acidifier. Quetiapine fumarate was selected as model weakly basic drug. Drug-excipients compatibility was studied by differential scanning Calorimetry (DSC) and fourier Transform Infrared (FTIR) studies**.** The effect of different formulation variables, namely, concentration of co-processed excipient and hardness of the tablet on the *in-vitro* release was studied using 3^2factorial design. Stability studies of the optimized formulations was carried out. The prepared co-processed excipient has complied all the established criteria for tablet formulation. There was no interaction seen among excipients while co-processing. The 24-hour dissolution profile of optimized batch and market product was comparable with the f2 value of 69. The short-term stability study shows no significant change in the physical characteristics and drug release pattern. The prepared co-processed excipient is novel and proved as a universal excipient for weakly basic drugs. Method of preparation of co-processed excipient wassolvent evaporation technique and was optimized for lab-scale production. The excipient has excellent flow property as well as compressibility. Any method of tableting from direct compression, wet granulation, and hot-melt extrusion, can be applied as per the necessity.

Key Words: Co-processed excipient, weakly basic drugs, HPMC, hydrogenated castor oil, anhydrous citric acid.
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Introduction

In spite of development of various kinds of novel dosage forms, tablets are still the most commonly used dosage form because of the ease of manufacturing, convenience in administration, accurate dosing and excellent stability. From all pharmaceutical products only tablets and capsules cover 80% of the market. Obviously, the ratio will be higher for tablets as the most famous and patient friendly oral dosage form. The demand of multifunctional excipients has increased in recent years due to increase in popularity of tablet dosage form [Saha S. et al. 2009]. The aim of this project is to prepare and evaluate a novel co-processed excipient containing HPMC K100M, HCO and anhydrous citric acid which can be utilized to prepare extended-release tablet dosage form of weakly basic drug.

Formulation of tablets may reserve many multi-step operations and much more accuracy and care are required to meet desired specifications and obtain a good product. This project aims to cut off the extra steps and operations which engage more accuracy and resources. Co-processing of more than one excipient of different category, to achieve a multipurpose excipient is a new field of research for a formulation scientist. Single component excipients do not always provide the requisite performance to allow certain active pharmaceutical ingredients to be formulated or manufactured adequately [Block LH et al. 2009]. Numerous research in co-process excipient is being carried out by scientist around the world. Gohel et.al. [Gohel MC et al. 2012]have developed multifunctional co-processed diluent consisting of microcrystalline cellulose (Avicel PH 102), crospovidone (Polyplasdone XL) and polyethylene glycol 4000 using melt granulation technique for the preparation of immediate release tablet dosage form.Kanojia et.al. [Neha Kanojia et al. 2013]have evaluated the need of modifying excipients to enable the delivery, manufacture, and development of various novel dosage forms. Patil et.al. [Atul P et al. 2013] have presented the use of co-processed excipient to overcome deficiencies occurring with general grade excipients. In this review, excipient innovations in the field of immediate release and controlled release formulations have been magnified. Gangurde et.al. [Avinash G et al. 2013] have developed and evaluated a novel directly compressible co-processed excipient for sustained release formulations by using Methocel K4M and Polyox WSR 301 through roller compaction technique. Gohel and Jogani [Gohel MC et al. 2005]have explained the importance of the functionality of the directly compressible adjuvants in the formulation of tablets. The review focused on the properties of the co-processed directly compressible adjuvants available in the market. Tang et.al. [Yong-Dan T et al. 2007] have presented that floating dosage forms enable the sustained delivery of drugs in the gastro-intestinal tract. In that study, a type of multi-unit floating gel bead was synthesized with calcium alginate, sunflower oil, and a drug of interest through an emulsification/gelation process.

Excipients with improved functionality can be obtained by enveloping new chemical excipients, new grades of existing materials and new combination of existing materials. The New combinations of existing excipients is an interesting option for improving excipients functionality as most of the formulations contain multiple excipients. A much broader platform for the manipulation of excipient functionality is provided by co-processing or particle engineering of two or more excipients. Co-processing is based on the novel concept of two or more excipients interacting at the sub particle level, the objective of which is to provide a synergy of functionality improvement as well as masking the undesirable properties of individual. [Mirani AG et al.2011] Co-processing leads to the formation of excipients that are granulated with superior properties, compared with physical mixtures of components or individual components. [Jacob S et al. 2007]. Co-Processed excipient provides formulation of tablets with low weight variation and good compressibility even at low dwell time. The need of co-processed excipients raised because of shortcomings of existing excipients. It is a combination of two or more excipients, designed to physically modify their properties in a manner not achievable by simple physical mixing, and without significant chemical change. Optimal use and excipients with multifunctional property can provide pharmaceutical manufacturers with cost-savings in drug development and help in drug formulations innovation.

Co-processing of previously accepted/established excipients is one of the ways through which new excipients are coming to market without undergoing rigorous safety testing of a completely new chemical. Co-processed excipients are usually developed to address the issues pertaining to flowability, compressibility and disintegration potential, with the filler–binder combination being the most commonly tried. The combination of excipients chosen for co-processing should be complement each other to mask the undesirable properties of individual excipients and at the same time retain or improve the desired properties of excipients. The main aim of co-processing is to obtain a product with added value related to the ratio of its functionality/price. Co-processing is interesting because the products are physically modified without altering the chemical structure. Moreover, the co-processed excipients lack the official acceptance in pharmacopoeia. For this reason, a co-processed excipient will not be accepted by the pharmaceutical industry until it exhibits significant advantage over physical mixture of excipients.

Many methods are available in literature for preparation of co-processed excipient such as granulation, spray drying, hot melt extrusion, solvent evaporation, roller compaction, dehydration, co-crystallization etc. Solvent evaporation method was adopted for preparation of co-processed excipient used in formulating extended-release dosage form of weakly basic drugs. Proper specifications and limits were established from repeated experiments or reported values in literature. The desired co-processed excipient was supposed to be such that it would have an excellent flow property and compressibility which are the heart of direct compression operation for tableting. To fulfill these needs, excipient has been evaluated for various parameters like angle of repose, Hausner ratio, Carr's index, particle size distribution etc. The prepared co-processed excipient would be utilized to prepare extended-release dosage form of weakly basic drugs. The specialty of this excipient is that it would be a universal excipient for all weakly basic drugs which are supposed to be formulated as extended release. The novel co-processed excipient has been designed such that less operational steps are required for industrial manufacture, less number of ingredients to be used, deduction in expenditure on inventory control, improve flow property and compressibility and improve dosage form compatibility.

Experimental

Sodium alginate, Polyox WSR 303, HPMC K4M, HPMC K 100M and Hydrogenated castor oil were obtained as a gift sample from Cadila Healthcare Limited. Ascorbic acid and citric acid were obtained from central drug house (P) Ltd (CDH).

Excipients for co-processing were selected by considering material characteristics and functionality requirements.Our aim was to prepare co-processed extended-release excipient for a weakly basic drug. Accordingly, we incorporated one hydrophilic excipient, one hydrophobic excipient and one weak acid as dissolution enhancer. From various hydrophilic excipient, we find HPMC K100M [Amaral MH et al. 2001] most suitable to meet our goal. Hydrogenated castor oil was selected as hydrophobic excipient for co-processing. Citric acid was selected as a dissolution enhancer for weakly basic drug and included in co-processing. The concentration of each individual excipient was optimized as per their most widely used concentration ratio.

Preparation of Co-processed excipient

HPMC K100M, Hydrogenated castor oil and anhydrous citric acid were weighted accurately in a quantity 4 g, 4 g and 2 g respectively. 100 ml mixture of isopropyl alcohol and dichloromethane in a ratio of 1:1 was prepared in a beaker. All ingredients were dissolved in solvent mixture to prepare clear viscous solution. This solution was evaporated at 40 °C for 2 hours. The dry mass was sifted through 100 # sieve. The angle of repose, carr's index and hausner ration was determined as per the method given in USP [USP 29th edition, 2006]. Average particle size was measured by microscopic method. [Parrot EL et al. 1987].

Particle size and morphology

Scanningelectronmicroscopy(SEM) isamethodforhighresolutionsurface imaging.TheSEMusesanelectronbeamforsurf aceimaging.Double-sidedcarbon tapewasaffixedonaluminumstubsoverwhicht hepowdersampleofCo-processed excipientsampleswasobservedformorpholog icalcharacterizationusingagaseous secondaryelectron detector.

FourierTransformInfrared Spectrophotometry (FTIR)study.

TheFTIRspectraofsampleswererecordedonth eonaPerkinElmer spectrumBXFTIR(PerkinElmer,Waltham,MA, USA)usingthepotassium bromide(KBr)disctechnique.Samplesequival entto2mg physical Mixture of all three Excipients and co-processed excipient wer emixedwith potassiumbromide (about100mg) inacleanglasspestle and mortar individually and were compressed to obtainapellet.Baselinewascorrectedandthes amples were scanned against a blankKBrpelletbackgroundatawavenumberr angingfrom 4000-400 $cm^{-1}$with a resolution of 1.0 cm^{-1}.

Differential ScanningCalorimetry

DSC measurements were performed with a Perkin Elmer Differential Scanning Calorimeter under nitrogen atmosphere. Appropriate amount of samples (~ 6 mg) were sealed in aluminum pans and heated upto 300°C at a scanning rate of 10°C/min.

Preparation of Quetiapine Fumarate extended-release tablets

Direct compression process was adopted for the preparation of quetiapine fumarate extended-release tablets. Drug , co-processed excipient and talc was sifted through 60 # sieve and mixed for 15 minutes in a double cone blender. After that the mixture was lubricated with magnesium stearate and mixed for 5 minutes.

Results and discussion

Physicochemical properties of co-processed excipient

Physicochemical properties of co-processed excipient are shown in table 1.

Physical properties of co-processed excipient	Established criteria	Observed value
Color	White to off-white	White to off white
Odor	None	None
Texture	Smooth, non-adhesive	Smooth, non-adhesive
Solubility	Soluble in IPA+DCM (1:1) mixture	Soluble in IPA+DCM (1:1) mixture
Optical Microscopy	Small Spherical to Ovoid Granules	Small Spherical to Ovoid Granules
Particle Size Distribution	100-150 µm	100-150 µm
Average Particle Size (Microscopic method)	-	126 µm
Carr's Index	< 18 %	14.4 % ± 0.3
Hausner's Ratio	< 1.25	1.16 ± 0.2
Angle of Repose	< 30 °	26 ° ± 0.5 °

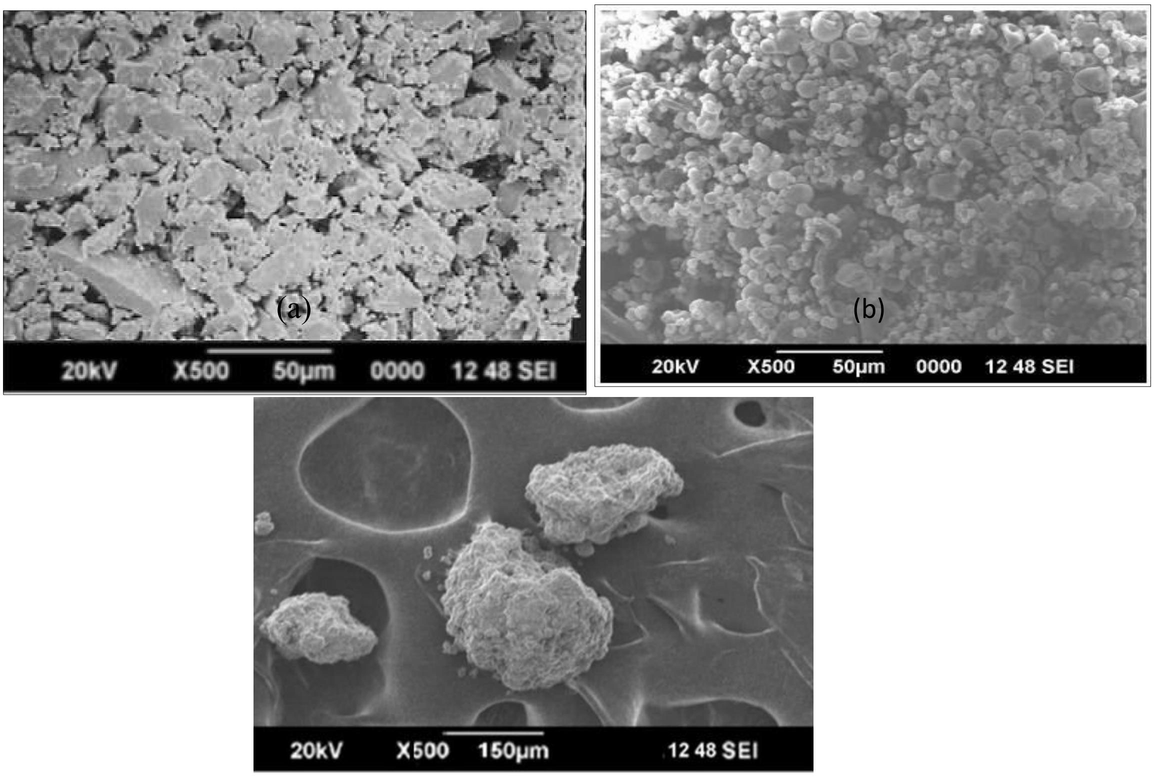
Table 1: Physicochemical properties of co-processed excipient

Above results indicates that the prepared co-processed excipient has excellent flow properties and is suitable for direct compression application.

Particle size and morphology

The SEM images of co-processed excipient are shown in figure 1. The imagesshowthatthereisnoparticle-particleaggregationbetween anytwodifferentexcipients.Morphologyofparticleissmootherthan individual excipient. Inphysical mixtureofallthreeexcipients,thereareflakesofHPMCK100Mwhichareflatin naturewhileinco-processedexcipient,regularshapeofparticleshasbeen achieved.

Fig. 1: ScanningElectronMicroscopy(SEM)of(a)Physicalmixtureofexcipients,(b)Co-processedexcipient(c)Singleparticleofco-processedexcipientinmagnification



(c)

FourierTransformInfrared Spectrophotometry (FTIR)study.

Allcharacteristicpeaksinthephysicalmixtureremainssignificantly unchangedwhichmeansthereisnosignificantchangeinthechemicalstructuresof individualexcipients.Theycanexhibitthesamephysicochemicalpropertiesinthe formofco-processedexcipientwhichtheyexhibitasphysicalmixture.FT-IR images of the physical mixture and co-processed excipients are shown in figure 2 and 3 respectively.

Fig. 2:FTIRimageofPhysicalMixtureofHPMCK100m,HydrogenatedcastoroilandCitricacidanhydrous.

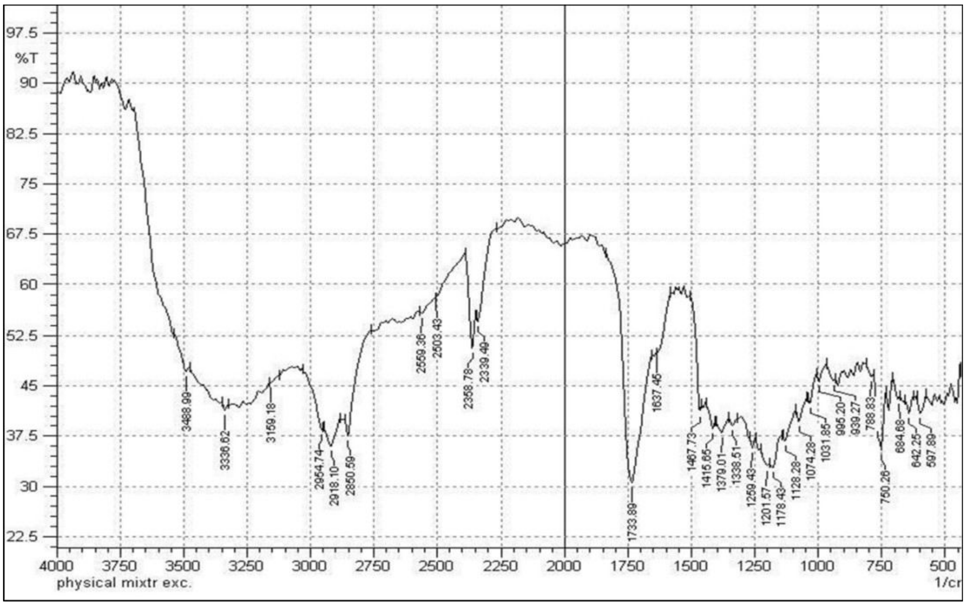
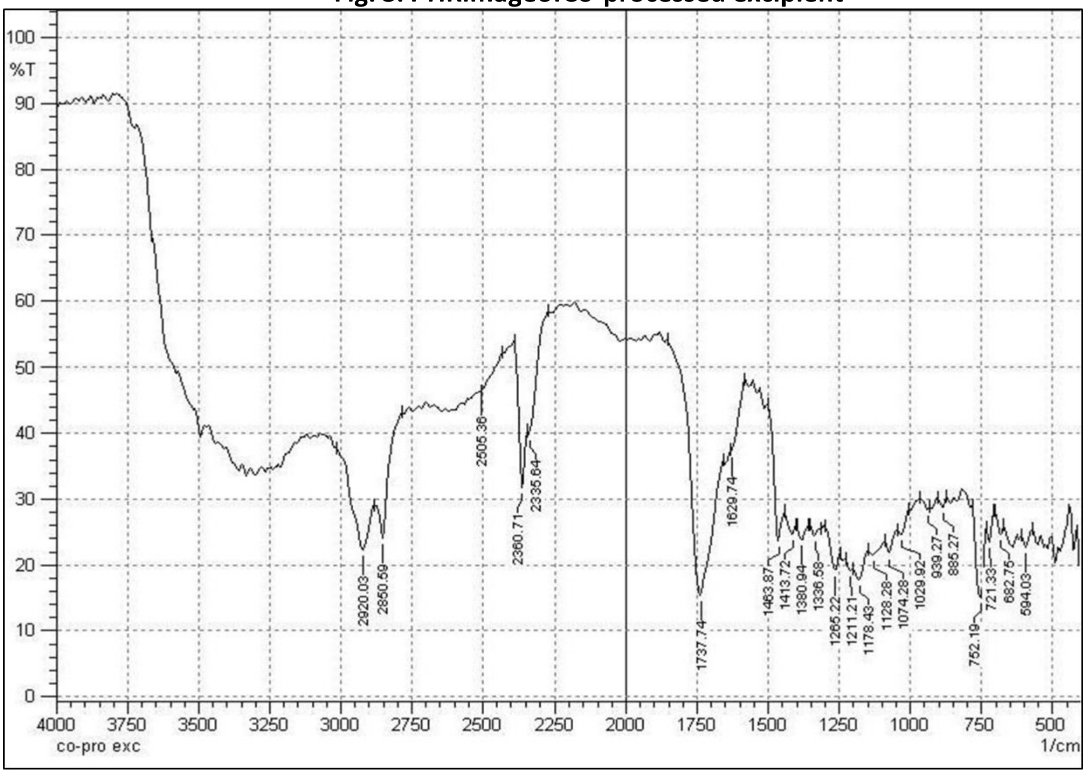


Fig. 3: FTIRimageofCo-processed excipient



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Differential ScanningCalorimetry

DSC thermographs of individual excipients and co-processed excipients are shown in figure 4. DSC study of the individual excipient and co-processed excipient reveals that there is no excipient-excipient interaction in co-processed excipient.

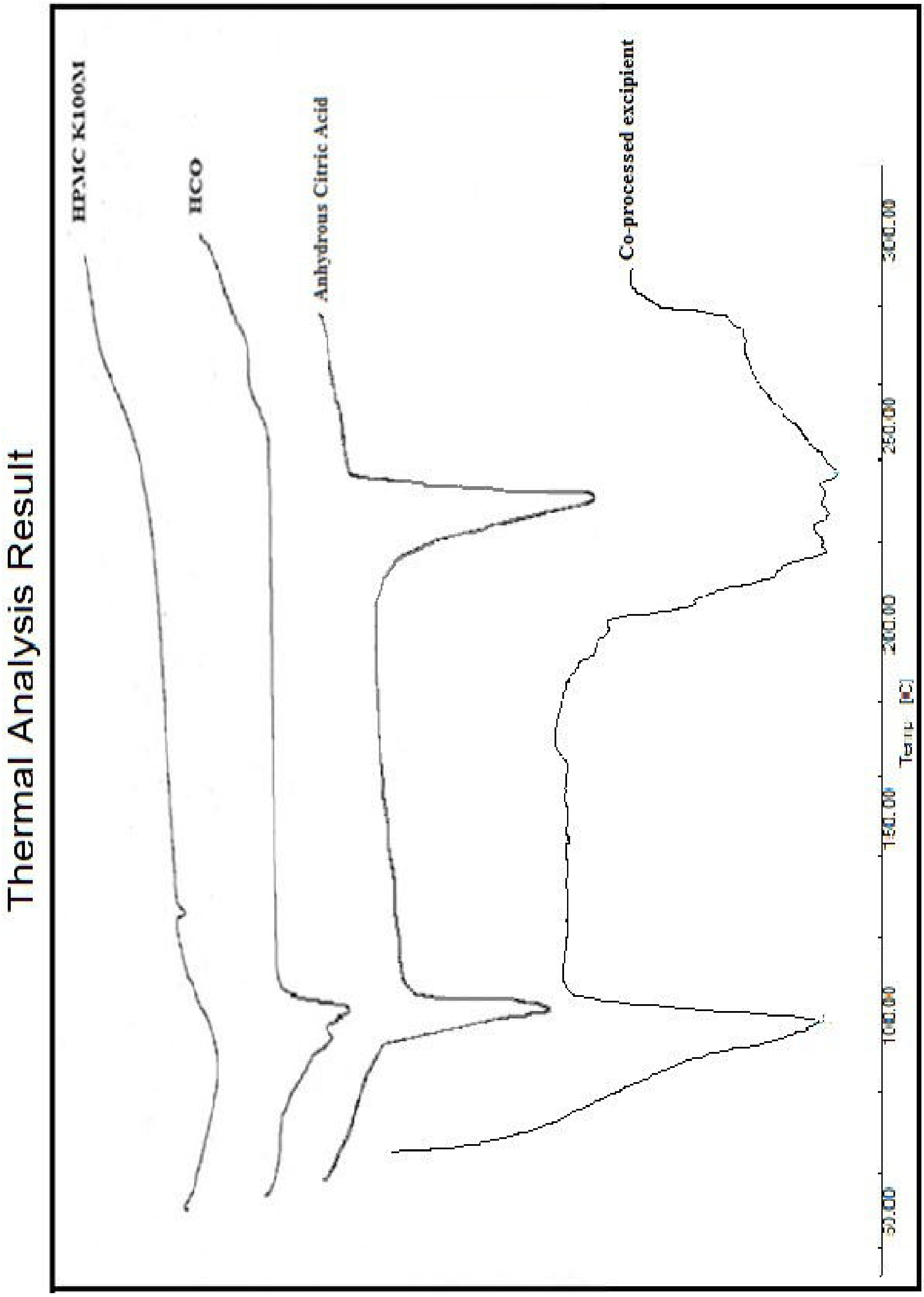

Fig.4:DSCthermogramof(a)HPMCK100M,(b)HCO,(c)Anhydrouscitricacidand(d)Co-processedexcipient

Gas Chromatography ofCo-processed excipient

Gas chromatography of co-processed excipient was performed to check the presence of residual solvent. Graph ofGC as shown in figure 5 reveals thatresidualsolvents present in the co-processed excipient is in traces andwithin the acceptable limits of ICH guideline.

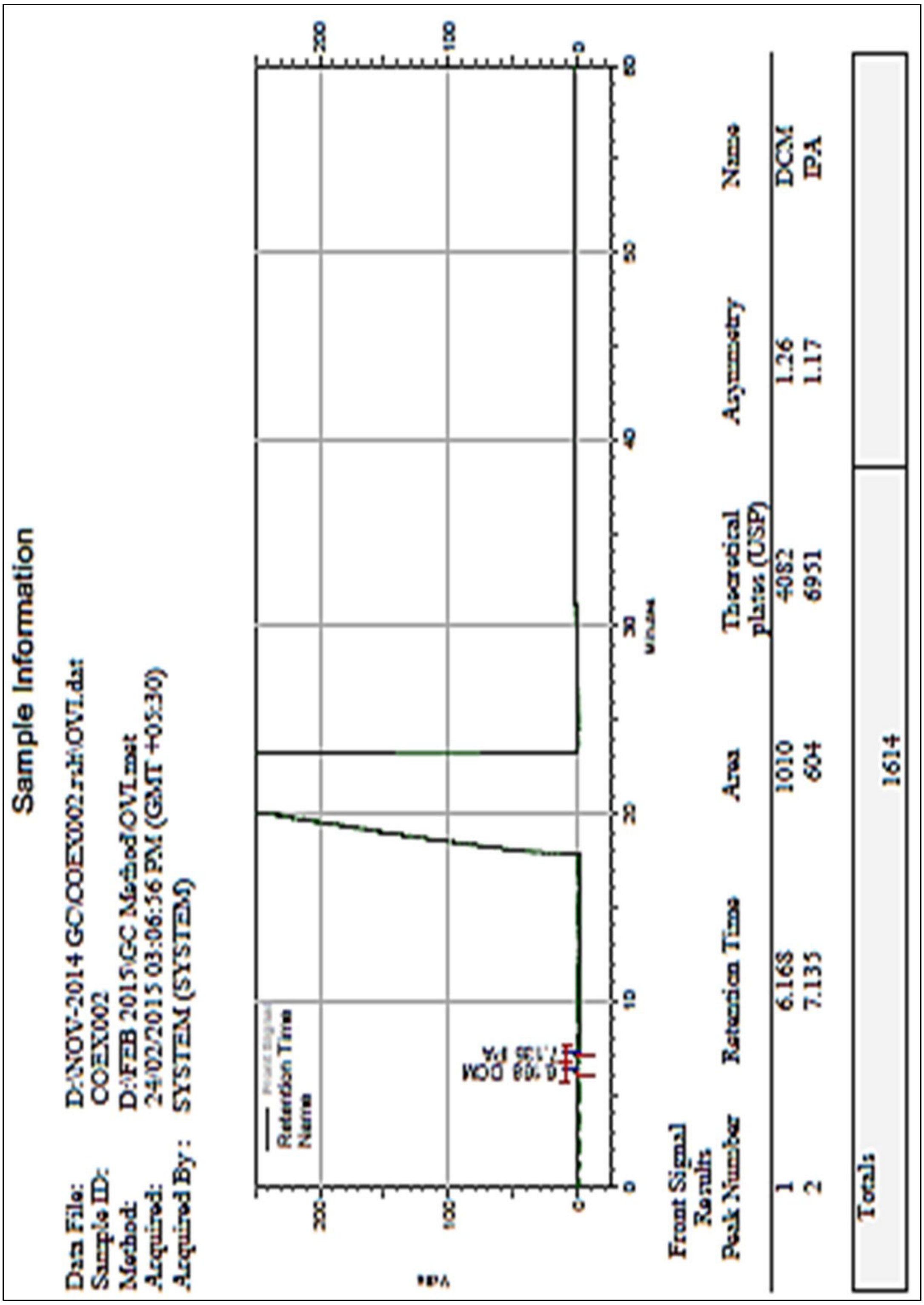

Fig. 5:Gaschromatogramofco-processedexcipientforremovaloforganicsolvent

Evaluation of QuetiapineFumarateextended-releasetablets

From the initial trials (data not shown), it was found that % of co-processed excipient and hardness of the tablet play a significant role in dissolution profile of drug. 3^2 full factorial design [Bolton S et al. 1987] was carried out to select the optimum composition of co-processed excipient and hardness of tablets. 3^2 full factorial design batches with two independent variables, three levels for each variable and one dependent variable are shown in table 2.As it is very important to control the drug release at 1 hour to match f_2 value, we kept Y1 (dissolution at 1 hour) as dependent variable. The dissolution media was 0.05 M citric acid and 0.09 N sodium hydroxide (pH 4.8) for up to five hours. At five hours, pH adjusted to 6.6 by adding 100 ml of 0.05 M dibasic sodium phosphate and 0.46 N sodium hydroxide. [Dissolution method database]. Table 3 shows the composition of each factorial design batch and drug release observed at 1 hour.

Factorial design batches	X1 (Tablet hardness)	X2 (% of co-processed	X1*X1	X2*X2	X1*X2	Y1 (Drug release at 1 hour)
QF1	-1	-1	+1	+1	+1	30
QF2	-1	0	+1	0	0	24
QF3	-1	+1	+1	+1	-1	18
QF4	0	-1	0	+1	0	28
QF5	0	0	0	0	0	21
QF6	0	+1	0	+1	0	17
QF7	+1	-1	+1	+1	-1	23
QF8	+1	0	+1	0	0	18
QF9	+1	+1	+1	+1	+1	14

Table 2:3^2 Full Factorial design batches and responseY1forall batchesofQuetiapineFumarates

Ingredients	QF1	QF2	QF3	QF4	QF5	QF6	QF7	QF8	QF9
Quetiapine Fumarate	230	230	230	230	230	230	230	230	230
% Co-processed excipients (mg quantity) (X1 Variable)	50 (230)	60 (345)	70 (537)	50 (230)	60 (345)	70 (537)	50 (230)	60 (345)	70 (537)
Magnesium stearate	9.2	11.5	15.3	9.2	11.5	15.3	9.2	11.5	15.3
Talc	9.	1	1	9	11.	15.	9	1	15.

	2	1.5	5.3	.2	5	3	.2	1.5	3
Total weight of tablet	478.4	598.0	797.3	478.4	598.0	797.3	478.4	598.0	797.3
Tablet hardness (kg/cm^2) (X2 variable)	5.0 (± 0.4)			6.0 (± 0.4)			7.0 (± 0.4)		
% Drug release at 1 Hr (Y1)	30	24	18	28	21	17	23	18	14

Table 3: Formula,Independentvariables,and dependent variablesforall9 factorial batchesofQuetiapineFumarate

From the regression data as shown in table 4, it can be concluded that both X1 and X2 have significant impact (p value < 0.01) on dissolution at 1 hour. The reduced model equation derived from the regression analysis is Y1 = 21.556 – 2.833 X1 – 5.333 X2 + 0.75 X1X2

Variables	**Coefficients**	**P-value**
Intercept	21.555	1.40041E-05
X Variable 1 (X1)	-2.833	0.000993158
X Variable 2 (X2)	-5.333	0.000151193
X Variable 3 (X1*X1)	-0.833	0.115203524
X Variable 4 (X1*X1)	0.666	0.176677466
X Variable 5 (X1*X2)	0.75	0.067865876
Multiple R	0.998	
R Square	0.996	
Adjusted R Square	0.989	
Standard Error	0.535	
Observations	9	

Table 4:Analysisofregressiondataforall factorial batchesofQuetiapineFumarate

Y1 value ofQF9batch is closer to that oneof marketedproduct (Table 6). QF9 batch was selected for further study. The above derived equation was validated by using the composition of QF9 batch as shown in table 5. Complete dissolution was carried out for this QF9 batch up to 24 hours. The predicted and experimental value of Y1 obtained was 13.97 and 14 percentagerespectively that indicates the validity of the equation.

Sr. No.	Ingredients	Quantity
1.	Quetiapine Fumarate	230 mg
2.	Co-processedexcipient	537 mg
3.	Magnesium stearate	15.3 mg
4.	Talc	15.3 mg
Total weight		797.3 mg

Table 5:OptimizedbatchforQuetiapineFumarateERTablet

Dissolution data of Seroquel 200 was obtained from the NDA (new drug approval) reports available online at www.fda.gov. [Drug database]. The calculation of f_2 value of QF9 batch and Seroquel 200 is shown in table 6. The observed f_2 value is 69.25, that indicates that the dissolution profile of test and reference product is similar. The graphical comparison of dissolution profile of QF9 batch and Seroquel XR 200 is shown in fig 6.

INGREDIENTS	OPTIMISED FORMULA (QF9 batch)	SEROQUELXR200
Dissolution (N=3)	0.05 M citricacid and 0.09 N Sodium Hydroxide (pH 4.8). [SolutionA].At 5 hours, pH adjusted to6.6 by adding100 ml of 0.05 MdibasicSodium Phosphate and 0.46 N Sodium Hydroxide. [Solution B].	
Time(in Hr)	%CumulativeDrugRelease	
1	14	13
2	18	23
4	31	41
6	55	56
8	62	66
1	75	74
1	82	78
1	90	88
2	95	95
2	97	100

2	$F_2 = 50 * \log [\{100/\sqrt{(1+ [\Sigma(R_t - T_t)/n])}\}]$	
F_2 valuewith SEROQUELXR 200	**69.25**	--

Table 6:Dissolution profile comparison between QF 9 and Seroquel XR 200

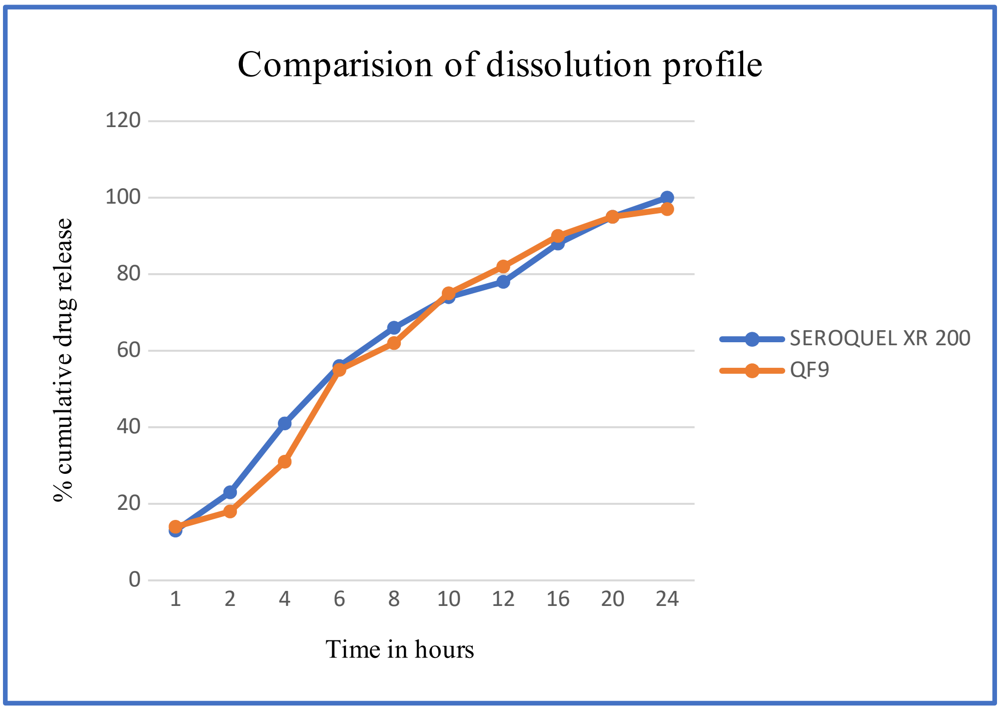

Fig.6:DissolutionProfileofMarketedProductv/sOptimizedBatch

Short-termstability study.

AsperICHguidelinesforthestabilityofsolidoralpharmaceuticalproducts, any prepared formulation should be tested for its stability. Short termstability study was performed for3month. TheoptimizedbatchQF9was subjected for shorttermstability study. Tablets were stored in alu-alu pouch and hermetically sealed. Storage conditions and humidity conditions adopted was 40 ± 2 ° C and 75 ± 5 % RH. At intervals of everyone week,thetablets were visually examined for any physical changes. The dissolution data of initial and after storage period are shown in table 7. Studentt–testbetweenbeforeandafter3 months of storage showed insignificant difference(t_{cal}<$t_{tab.}$). It confirms that there must be adequate storage container.

Time (in Hrs)	% Cumulative drug release	
	Initial	**After3 months**
1	14	13
2	18	17
4	31	31

6	55	54
8	62	61
10	75	74
12	82	81
16	90	90
20	95	94
24	97	96

Table 7:DissolutionProfilesofOptimizedBatch QF9 after 3-monthsstorage

Conclusion:

The prepared co-processed excipient is novel and proved as a universal excipient for weakly basic drugs. It has all the characteristics suitable for tablet dosage form. Method of preparation of co-processed excipient was solvent evaporation technique and it is optimized for lab-scale production. The concentration of each individual excipient was optimized as per their most widely used concentration ratio. The excipient has excellent flow property as well as compressibility. As the presented co-processed excipient contain both hydrophilic and hydrophobic excipient, any method of tableting from direct compression, wet granulation, and hot-melt extrusion, can be applied as per the necessity. An optimized formula for any weakly basic drug can be achieved with minimal trial batches. It provides easy technique for tablet formulation and manufacturing.

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References:

1. Saha S, Shahiwala AF. Multifunctional coprocessed excipients for improved tabletting performance. Expert Opin Drug Deliv 2009; 6:197-208.
2. Block LH, Moreton RC, Apte SP, Wendt RH, Munson EJ, Creekmore JR, et al. Co-processed excipients. In: Pharmacopeial forum. vol. 35. Maryland, USA: United States Pharmacopeia Convention Inc; 2009, p. 1026 -8.
3. Gohel MC, Patel TM, Parikh, RK, Parejiya PB,Barot BS and Ramkishan A; Exploration of Novel Co-processed Multifunctional Diluent for the Development of Tablet Dosage Form, *Indian J Pharm Sci.* September, 2012; 74(5): 381-386.
4. Neha K, Loveleen K, Manju N and Rajni B; Modified Excipients in Novel Drug Delivery: Need of the Day, Journal of Pharma. Techno., Research and Management, May 2013; 1: 85-107
5. Atul P, Subrata Kand Ganga S; A Review On Co-processed Excipients: A Novel Approach In Formulation Development, *International Journal Of Review Article Pharmaceutical Innovations,* September – October, 2013; 3(5): 25-41
6. Avinash G, Rahul KP, AjayKumar S, Purnima DA; A Novel Directly Compressible Co-Processed Excipient for Sustained Release Formulation, *Journal of Applied Pharma. Science*, September, 2013; 3 (09) :89-97
7. Gohel MC & Jogani PD, A review of co-processed directly compressible excipients, *J Pharm Pharmaceut Sci*, 2005; 8(1):76-93
8. Yong-Dan T, Subbu SV, Freddy Y.C. Boey, Li-Wei Wang; Sustained release of hydrophobic and hydrophilic drugs from a floating dosage form, *International Journal of Pharmaceutics*, 2007; 336 :159–165
9. Mirani AG, Patankar SP, Borole VS, Pawar AS, Kadam VJ. Direct compression high functionality

excipient using coprocessing technique: A brief review. Curr Drug Deliv 2011; 8:426-35.
10. Jacob S, Shirwaikar A, Joseph A, Srinivasan K. Novel co-processed excipients of mannitol and microcrystalline cellulose for preparing fast dissolving tablets of glipizide. Indian J Pharm Sci 2007;69:633-9.
11. Amaral MH, Sousa Lobo JM and Ferreira DC; Effect of Hydroxypropyl Methylcellulose and Hydrogenated Castor Oil on Naproxen Release From Sustained-Release Tablets *AAPS PharmSciTech.* Jun 2001; 2(2), Pp-14–21.
12. United States Pharmacopoeia. 29th ed. Rockville, MD: The United States Pharmacopeial convention Inc; 2006. p. 3017-20.
13. Parrot EL. Milling. In: Lachman L, Lieberman HA, Kanig JL, editors. The Theory and Practice of Industrial Pharmacy. 3rd ed. Bombay: Varghese Publishing House; 1987, p. 21-46.
14. Bolton S. Statistical Application in the Pharmaceutical Sciences. In: Lachman L, Lieberman HA, Kanig JL, editors. The Theory and Practice of Industrial Pharmacy. 3rd ed. Bombay: Varghese Publishing House; 1987, p. 243-89.
15. Dissolution method database. https://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults.cfm retrieved on 10 July 2014.
16. Drug databases. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=022172 retrieved on 10 July 2014.