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Original Article

Pectin-Xanthan Gum as Natural Co-Processed Excipient for Formulation of Colon Specific Tablet

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ABSTRACT

The objectives of study is coprocessing of excipients provides products with superior properties in comparison to their parent excipients, alone or as a physical mixture. Coprocessing of pectin and xanthan gum was carried out A series of tablet batches coded F1 to F9 were prepared using coprocessed excipients and other batch coded A1 were prepared using physical mixture of pectin and xanthan gum. Compatibility study was performed using DSC and FTIR. From dissolution study, it could be concluded that Formulation A1 exhibited 80.64% drug release in 24 hr, while formulation F9 showed 92.34 % drug release in 24 hr. It revealed that formulation containing co-processed excipients showed improved performance compared to physical mixture formulation and it was due to its amorphous nature which shows more solvent affinity due to less degree of crystalline lattice. Hence from the physicochemical evaluations of all colon specific tablet formulations, it was concluded that formulation F9 was observed to be optimized formulation.

Key Words: Pectin,Xanthan gum, Coprocessed excipients, Colon Specific Drug Delivery

1. INTRODUCTION

Oral drug delivery is the most desirable and ideal method of administering therapeutic agent for their systemic effects [1]. Oral medication is investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, low cost, easiest and cheapest to package. Now a days tablet is one of the most preferred dosage form because of its ease of manufacturing, convenience in administration, accurate dosing, stability compared with oral liquids and more tamperproof than the capsule. There are different types of formulation but conventional release formulations provide clinically effective therapy by maintaining the required balance of pharmacokinetic and pharmacodynamic profiles

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with an acceptable level of safety to the patient [2]. Direct compression is a method by which tablets are compressed directly from the powder blends of active ingredients with suitable excipients. In simple terms, the direct-compression process is directly influenced by the properties of the excipients. The physic-mechanical properties of excipients that certify a strong and successful process are good flow ability, good compressibility, low or no moisture sensitivity, low lubricant sensitivity and good machine ability even in high-speed tableting machinery with reduced stay times.

Coprocessing of excipient is a combination of two or more established excipients by an appropriate process. Coprocessing is based on the novel concept of two or more excipients interacting at the subparticle level, to improve functionality as well as masking the undesirable properties of individual excipients [3].There are various different methods for coprcessing.

The colon is a site where both local and systemic drug delivery can take place. A local means of drug delivery could allow local treatment of inflammatory bowel disease e.g ulcerative colitis or crohn's disease such inflammatory condition are usually treated with glucocorticoid and sulphasalazine treatment will be more effective if the drug substance are targeted directly at the site of action in the colon [4].

Colon specific systems could also be used in conditions in which diurnal rhythm is evident e.g. asthma, rheumatic disease, ulcer disease and ischemic heart disease. The incidence of asthmatic attack are, e.g., greatest during the early hours of the morning. As dosage forms reside for longer duration in the large intestine than in the small intestine, colon-specific formulation could be used to prolong drug delivery [5].

Developing a coprocessed excipient involves:

1. Identifying the group of excipients to be coprocessed by carefully studying the material characteristics and functionality requirements,
2. Selecting the right proportions of various excipients to be coprocessed
3. Choosing a suitable method for coprocessing and post processing methods to achieve the desired material characteristics.[6]

Different methods can be used for coprocessing of pharmaceutical excipients depending on heat stability, compatibility, solubility in particular solvents, crystallinity and other physical properties of the excipients to be used in combination. Various methods like wet granulation, dry blending, compaction- formation of drugs, melt granulation, formation of agglomerates, formation of thin films and sifting and spray drying can be used for manufacturing coprocessed excipients.[7]

Coprocessing of excipients:

Coprocessing of excipient pectin and xanthan gum was carried out. Steps are as follows

a) Solubalisation:

Pectin and xanthan gum were taken in appropriate weights. As both the excipients are freely soluble in distilled water at 60°C, both excipients were poured gradually to prevent formation of clumps in 500 ml beaker containing 70 methanol and 30 ml distilled water and stirring was continued to make them soluble.

b) Solvent evaporation:

The beaker containing excipients mixture was kept on magnetic stirrer at three different speeds (300 rpm,400 rpm, and 500 rpm) and temperature was maintained between 30 to 50°C for 24, 36, 48 h till the complete solvent was evaporated. Precaution was taken that a beaker containing excipients mixture was wrapped with aluminium foil after solvent evaporation till further processing to prevent microbial growth.

c) Drying and Sifting:

The wet coherent mass was air dried for 2 to 3 h till it was completely dried. And the dried coprocessed excipient was sifted through # 44 mesh sieve, again dried for 30min. at the temperature of 40°C and stored in airtight container till further use. Co-processing of pectin and xanthan gum was carried out as per concentrations given in table no.1:

Table 1: Excipients ratio for coprocessing

Xanthan Gum (gm)	Pectin (gm)				Solvent (70:30)
	20%	30%	40%	50%	
9	6	9	12	15	Ethanol: Water

2. EXPERIMENT

Ibuprofen

Ibuprofen was a gift sample from cure pharma pvt. Ltd. All other materials used were of Pharmacopoeial grade.

1. Formulation of colon specific tablets:

1.1. Preparation of Tablets:

All the ingredients except glidant and lubricant were weighed accurately and passed through sieve no 40, and were taken in morter and mixed thoroughly for 15 min. A small quantity of starch paste (5%) was added to make cohesive mass. This cohesive mass was then passed through a sieve no 22 then weighed quantity of glidant andlubricant was added. The prepared granules were dried at 40°C for 30 min. in hot air oven (singhla Scientific, Ambala cantt.). This blend was compressed by using 14 mm round flat -faced punch using KBr press tablet compression machine.

Formulations (A1) were prepared by using pectin and xanthan gum individually (without coprocessing) to analyse the exact effect of coprocessing. Pectin was used in the concentration from 20-50 % to totalweight of formulation, while concentration of xanthan gum was kept constant to 30 % throughout the formulation.

The formulae (F1-F9) for development of colon specific tablets of ibuprofen usingcoprocessed excipient in the

proportions of 60% compared to total formulation weight, are as given in the formulae for the development of colon specific tablets using both coprocessed and non coprocessed excipients is given in table no.2.

Formulation table:

Table 2: Formulation table for ibuprofen colon specific tablets

Ingredients	Formulation										
	Time (48 h)		Temp (30° C)			Temp (40°C)			Temp (50°C)		
	RMP		300	400	500	300	400	500	300	400	500
	Batch	A1	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ibuprofen	300		300	300	300	300	300	300	300	300	300
Co-processed excipients	-		516	516	516	516	516	516	516	516	516
Pectin	434.35		-	-	-	-	-	-	-	-	-
Xanthan Gum	81.65		-	-	-	-	-	-	-	-	-
Magnesium Stearate	16		16	16	16	16	16	16	16	16	16
Talc	16		16	16	16	16	16	16	16	16	16
Total	**848**		**848**	**848**	**848**	**848**	**848**	**848**	**848**	**848**	**848**

*** All quantities are in mg. Formula for one tablet is shown in table.**

2.Characterization of Ibuprofen:

2.1.Description

Ibuprofen was found to be white, odourless, amorphous powder having slight bitter taste.

2.2. Solubility of drug:

Ibuprofen was found to be slightly soluble in water and freely soluble in methanol.

2.3.Melting point of drug

The melting point of Ibuprofen was found to be in the range of 80-84°C.

2.4.Determination of λ max (UV scanning) of Ibuprofen

As shown in figure 3, the absorption maximum of pure ibuprofen was found to be at wavelength 221 nm in 1.2 pH and phosphate buffer pH 6.8 and 7.4

2.5. Differential scanning calorimetry (DSC)

Such sharp endothermic peak signifies that ibuprofen, xanthan gum, Pectin, Ibuprofen and Coprocessed excipients used was in pure state. The DSC thermogram is shown in Figure1,2,3,4.

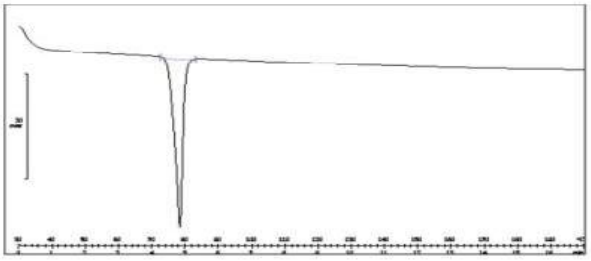

Fig 1: DSC thermogram of ibuprofen

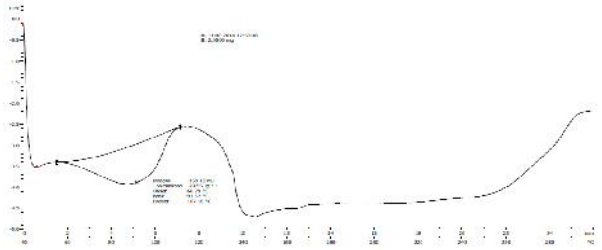

Fig 2: DSC thermogram of Xanthan gum

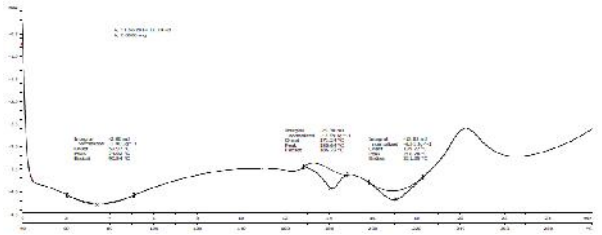

Fig 3: DSC thermogram of Pectin

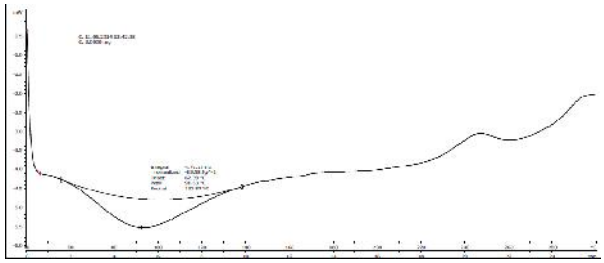

Fig 4: DSC thermogram of Coprocessed excipient

2.6.FTIR spectroscopy

The FTIR spectrum of ibuprofen, Xanthan gum, Pectin and Coprocessed excipient is shown in Figure 5,6,7,8.

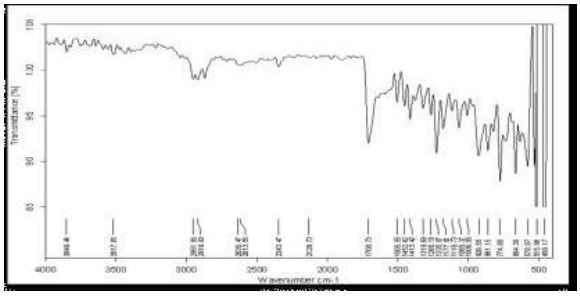

Fig 5: FTIR spectrum of ibuprofen

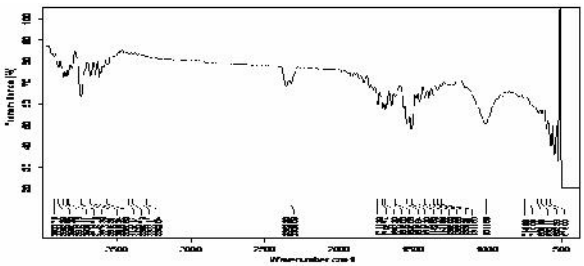

Fig 6: FTIR spectrum of Xanthan gum

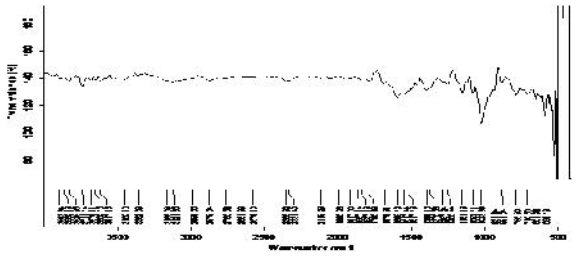

Fig 7: FTIR spectrum of Pectin

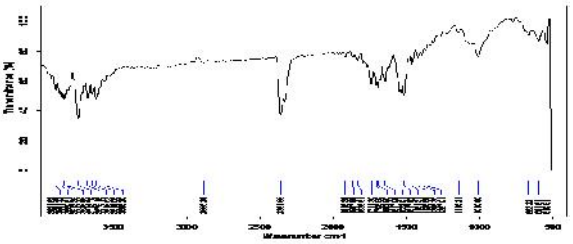

Fig 8: FTIR spectrum of Coprocessed excipient

2.7. X-ray diffraction study:

The XRD analysis of pectin, xanthan gum and their coprocessed product was carried out to study their morphological pattern. It is given in figure no. 9,10,11.

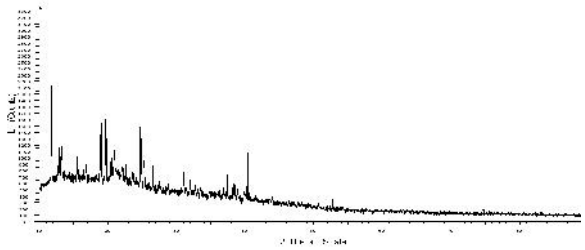

Fig 9: XRD analysis plot of pectin

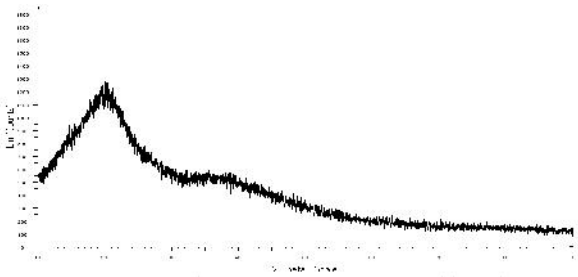

Fig 10: XRD analysis plot of Xanthan gum

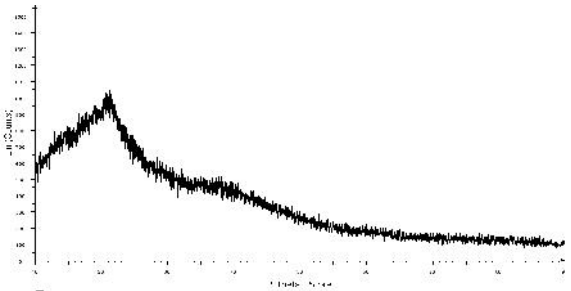

Fig 11: XRD analysis plot of coprocessed product

The XRD pattern of pectin, Xanthan gum and coprocessed product showed intense and sharp peak at intensity 2150,1300,1100. Pectin and Xanthan gum shows crystalline but was decrease in the crystallinity of coprocessed excipient.

The relative degree of crystallinity (RDC) was calculated according to equation:

$RDC = I_{Sample} / I_{reference}$

Where I_{sample} is the peak height of highest intensity of sample i.e. coprocessed product and $I_{reference}$ is the peak height at the same angle for the reference i.e. pectin with the highest intensity.

The RDC value of corresponding coprocessed excipient was found to be 0.51.Thus the XRD analysis revealed that there was reduction in the diffraction intensity of coprocessed excipient. This indicates reduction in the crystallinity of coprocessed excipient.

3. RESULTS AND DISCUSSION

3. Preformulation studies of coprocessed and non-coprocessed powder blends:

The blended mixture which was ready for compression, was examined for angle of repose [10], bulk density [9,] tapped density, Carr's index(CI) [11], Hausner's ratio(HR). According to literature survey powders with CI values between 5% - 18% were suitable for producing tablets via direct compression and those with HR values below 1.25 and angle of repose below 20°Cexhibits excellent flow, while values in between 20°-30°C indicate good flow properties of powders.

The bulk density of all formulations containing both non coprocessed and coprocessed excipients was found to be in the range of 0.2523 to0.5470 gm/ml, whereas the tapped density was observed between 0.2790to0.7120 gm/ml. From the values of bulk density and tapped density the values for Carr's index and Hausner's ratio were calculated. The values for Carr's index were found between6.92 to23.07. The values for Hausner's ratio were found to be less than 1.25. Angle of repose was found to be less than 25^0. All these values indicate good flow properties of powder blend, uniform die fill and better compression ability. Therefore, from this data so obtained, it was decided to go for direct compression of tablets from the powder blends. [12, 13]

4. Evaluation of ibuprofen Colon specific formulations:

4.1. Compatibility study:

Compatibility study of drug with excipients was carried out using DSC and FTIR analysis. Results obtained are as discussed below:

4.2. DSC:

DSC thermograms of representative formulation A1 and F9 are as given in figure 12and 13 respectively

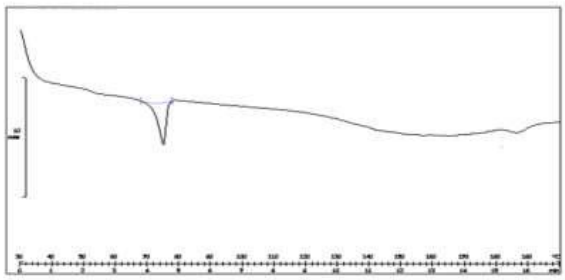

Fig 12: DSC thermogram of representative formulation A1

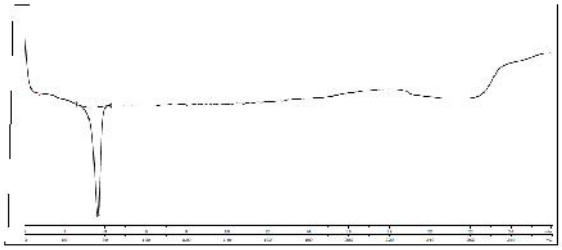

Fig 13: DSC thermogram of representative formulation F9

From the figures 12 and 13, it was observed that the DSC thermograms of representative formulations exhibited sharp endothermic peaks at 75.87°c which was close to melting point of ibuprofen. Thus from the DSC studies it was clear that there was no incompatibility between drug and excipients.

4.3. FTIR:

FTIR spectra of representative formulation A1 and formulation F9 are given in figure 14 and 15 respectively

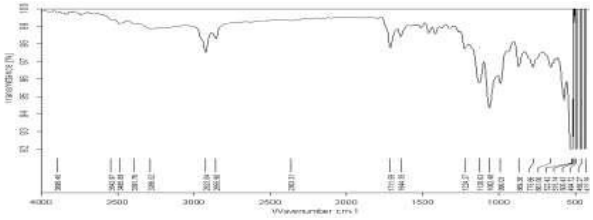

Fig 14: FTIR spectrum of representative formulation A1

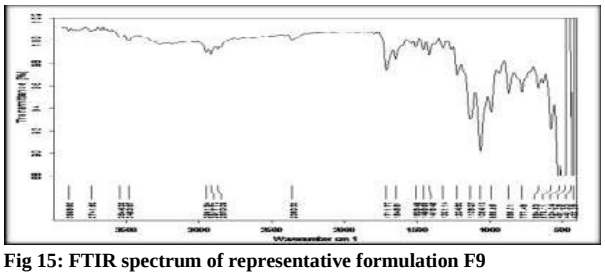

Fig 15: FTIR spectrum of representative formulation F9

FTIR spectra of representative formulations were found to contain the same peaks as that found in pure drug, and no any additional peak was observed in formulations FTIR. DSC thermograms of pure drug and the representative formulations exhibited a sharp endothermic peak near to the melting point of drug, revealing that no incompatibility existing between the drug and the excipients.Thus from both FTIR spectra and DSC thermograms, it could be concluded that there exists compatibility between the drug and the excipients.

5. Physicochemical evaluation:

Physicochemical evaluation of both coprocessed and non coprocessed formulations was carried out, in that weight variation, hardness, friability, diameter, thickness, drug content, and in-vitro dissolution study of tablets was carried out.

The thickness and diameter of all formulations containing both excipients was found to be uniform (table no 25) as it was obtained in the range of 5.00 to 5.05 mm and 13.02 to 13.04 mm respectively. Drug content of all formulations was observed between 97.90 to 99.56. All the formulations passed the test for weight variation. None of the tablet was found to deviate from the average weight of tablets. Hardness test for all formulations was carried out and they were obtained in the range of 6.1 to 6.52 kg/cm^2. Test for friability was conducted for all formulations, % friability was found to be in the range of 0.51 to 0.69

The values for thickness and diameter signify uniformity and it was due to uniformity in die fill, good flow properties, uniform pressure and appropriate punch movement. Drug content for all formulations showed uniformity which indicated that there was an uniform flow and uniform distribution of drug. Weight variation tests for all formulations showed weight variation with deviation less than ± 5, which complies with I.P specification and signifies that there is uniformity in flow of powder blend which leads to uniform die fill. Hardness for all formulations was observed to be proper, which signify that tensile strength of all formulations was maintained after compression. Friability test for all formulations indicated that % friability was less than 1%, which complies with the I.P specification and reveals that all formulations have possessed good physical strength and can withstand the mechanical shocks that can be observed during handling, shipping and transportation.

6. In vitro dissolution study:

Comparative difference can be observed from figure

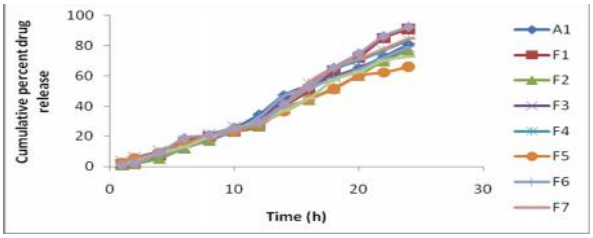

Fig 16: Comparative Plot of Dissolution profiles of Ibuprofen Colon specific tablet

Dissolution study was carried out using USP dissolution apparatus type II with paddle speed of 100 rpm using 900 ml acidic buffer solution pH1.2 and phosphate buffer solution pH 6.8 and 7.4 as dissolution medium.

By observation of table no 16, it can be concluded that all formulations showed maximum drug release, meanwhile formulation F9 showed maximum drug release (92.34%) within 24 h. Formulation A1 showed maximum drug release (80.64%) within 24 h. It means that co-processed formulation showed improved performance compared to respective physical mixture formulation.

Observations suggested that formulation A1 showed less drug release compared to formulation F9. It revealed that non coprocessed formulation, due to its crystalline nature shows less solvent affinity due to more degree of crystalline lattice. Hence, as compared to non co-processed formulations, coprocessed formulations have more amorphous nature which enabled them to undergo easy dissolution which resulted in improved drug release.

4. CONCLUSION

Coprocessing of excipients provides products with superior properties in comparison to their parent excipients, alone or as a physical mixture. Coprocessing is primarily aimed at addressing the issues of flow ability, compressibility, and disintegration potential. Thermal studies involving DSC and IR spectral studies revealed, the lack of chemical interaction between the two excipients after coprocessing. The XRD study indicated reduction of crystalline nature of these excipients after coprocessing. The coprocessed excipient showed improved functionality in terms of bulk density, tapped density, percent compressibility and angle of repose. Physico-chemical characteristics of powder blends were determined and were found to be satisfactory. A series of tablet batches coded F1 to F9 were prepared using coprocessed excipients and other batch coded A1 were prepared using physical mixture of pectin and xanthan gum. Compatibility study was performed using DSC and FTIR, which concluded that integrity of representative formulations were maintained as there was no any chemical alteration between drug and excipients. Physicochemical evaluation of finished dosage form reveals that physical appearance of all formulations was appropriate, while test for weight variation and friability complied with the official specifications.

From dissolution study, it could be concluded that Formulation A1 exhibited 80.64% drug release in 24 hr, while formulation F9 showed 92.34 % drug release in 24 hr. It revealed that formulation containing co-processed excipients showed improved performance compared to physical mixture formulation and it was due to its amorphous nature which shows more solvent affinity due to less degree of crystalline lattice. Hence from the physicochemical evaluations of all colon specific tablet formulations, it was concluded that formulation F9 was observed to be optimized formulation.

5. FUTURE PERSPECTIVES

The particular phenomenon of coprocessed excipient is a field having vast scopefor development of excipient with desirable property for compression as well for specificmethod and formulation. The limitations of existing excipients for new rapidlydeveloping API's can be overcome. A deeper understanding of their solid-state propertiesand its impact on excipient functionality is further going to fuel this trend. Functionalities,unavailable to the formulator, can now be incorporated into the product by judiciouschoice of high-functionality excipients. The process also opens opportunity fordevelopment and use of single multifunctional excipient rather than multiple excipients informulation. Now a day's many excipient are directly coprocessed with API's to developcomposition ready for direct compression. The newer excipients are required to becompatible not only with the latest technologies and production machineries, but alsowith the innovative active principles such as those originating from biotechnology. Theability of a large number of excipients for coprocessing gives surety of production oftailor made designer excipients to address specific functionally requirements. A greatersynergy between excipient manufacturers and the pharmaceutical manufacturer in thefuture is going to help in the development of tailor-made designer excipients complyingwith safety, performance, and regulatory issues.

6. ACKNOWLEDGEMENT

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