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Sustained release drug delivery systems of Cefuroxime Axetil

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ABSTRACT

The work focuses mainly on sustaining the release of Cefuroxime axetil by formulating them in to matrix tablets by using various matrix materials alone/ or in combination with ethyl cellulose (bees wax, lanatte wax, guar gum, xanthan gum, ethyl cellulose). The formulated tablets were subjected to evaluation by in vitro release studies. The release kinetics of the matrix tablet was also investigated in the work.

.**Key words**: Formulation, Cefuroxime axetil, Matrix.

INTRODUCTION

Traditional delivery system (TDS) is characterized by immediate and uncontrolled drug release kinetics. The purpose of controlled release system (CRS) is to maintain drug concentration in the blood or in target tissues at a desired value as long as possible in other words, they are able to exert a control on the drug release rate and duration[1].The basic rationale for controlled drug delivery is to alter the pharmacokinetic and pharmacodynamics of active moieties by using novel drug delivery system or by modifying the molecular structure and /or physiological parameters inherent in the selected route of administration[2].The primary objective of controlled drug delivery system is to ensure safety and to improve the efficacy of drug as well as patient compliance. It also does posses better plasma drug level and less frequent dosing. For a conventional dosage form, only dose (D) and dosing interval can vary and the therapeutic index can be maintained. In general dosing interval may be increased either by modifying the drug molecule to decrease the rate of elimination (kel) or by modifying the release of a dosage form to decrease the rate of drug absorption (ka)The term “matrix” indicates the three dimensional network containing the drug, polymers and other substances such as solvents and excipients required for the specific preparation.[3] Matrices can be prepared by mixing the drug, in the form of a thin powder, with the Pre-polymer/polymer and subsequently putting the whole mixture in the polymerization reactor and forming the matrix. Alternatively, matrix can be prepared in advance and then put in contact with highly concentrated drug solution able to swell the matrix

called as solvent swelling technique [4]. Among the various routes of administration, the oral route still remains as the most preferred and popular route of administration due to number of reasons. On the other hand, the oral route is limited constrained by short and variable GI transit time, fast-pass metabolism, limited absorption in the lower part of the GI tract, and the size of the system [5].Drug release kinetics may be affected by many factors such as polymer swelling, polymer erosion, dissolution/ diffusion characteristics, drug distribution inside the matrix ,drug polymer ratio and system geometry(cylinder, sphere and so on). Except for some rare cases, such as ophthalmic matrices, due to the dosing and the system of physical and chemical stability, Matrix system are stored in dry, shrunken state, i.e. without any liquid phase inside. In this condition, the drug, present in the dry polymeric network in form of microcrystals, nanocrystals or amorphous state, cannot diffuse through the network meshes. Upon contact with the release fluid, the polymer swells and drug dissolution can take place. For polymers showing transition temperature higher than the room temperature, the swelling process implies also the transition from the glassy dry state to rubbery swollen state.[6] The local solvent concentration greater exceeds a threshold value, polymeric chain unfold so that the glassy/rubbery polymer transition occurs and a gel like layer, surrounding the matrix dry core, begins to appear. This transition implies a molecular rearrangement of polymeric chain that tends to reach a new equilibrium condition as the old one was altered by the presence of incoming solvent. The time required for this rearrangement depends on the relaxation time t_T and the characteristic time of diffusion t_D of the solvent. [7]

If t_T is much lower than the characteristic time of diffusion t_D of the solvent, then solvent adsorption may be described by means of fick's law with a concentration dependent diffusion coefficient. On the contrary, if t_T is much greater than t_D, then fickian solvent adsorptions with constant diffusivity take place. When $t_T = t_D$ solvent adsorption does not follow fick's law of diffusion. In such case, the macroscopic drug release become anomalous or non-fickian. Thus, solvent absorption and drug release depends also on the polymer/solvent couple viscoelastic properties [8]. The glassy-rubbery transition enormously increases polymer chains mobility, so that mesh enlarges and the drug can be dissolved and diffuse through the gel layer. While microcrystals dissolution does not show particularly interesting aspect, dissolution of nanocrystals and amorphous drug exhibit a peculiar behavior. Indeed, as solubility depends on crystal size, because due to their small dimension are characterized by a higher solubility in aqueous medium with respect to the infinitely large crystal [9].There are two competing mechanisms involved in the drug release, Fickian diffusional release and relaxational release. Diffusion is not the only pathway by which a drug is released from the matrix, the erosion of the matrix following polymer relaxation also contribute to the overall release. The relative contribution of each component to the total release is primarily dependent on the properties of the given drug[4]. The release of a sparingly soluble drug from hydrophilic matrices involves the simultaneous absorption of water and desorption of the drug via a swelling controlled diffusion mechanism. As water penetrates into a glassy polymeric matrix, the polymer swells and its glass transition temperature is lowered. At the same time, the dissolved drug diffuses through this swollen rubbery region into the external releasing medium**.** This type of diffusion and swelling generally does not follow a Fickian diffusion mechanism. [10]

MATERIALS AND METHODS

Matrix tablets were formulated by using two methods

a) Direct compression technique- gum matrix materials
b) Melt granulation- waxy matrix materials

In melt granulation method, accurately weighed quantity of cefuroxime axetil was passed through 20 # sieve. Weighed quantity each formulations of wax (beeswax/lanette wax) melted in a china dish separately and cooled well. Before the time of congealing temperature of wax the sieved Cefuroxime Axetil was mixed. Then the hard mass was passed through 20# sieve. In direct compression method the sieved Cefuroxime Axetil and gum (guar gum / xanthan gum) of each formulation are mixed separately in a mortar. The lubricant was added to the powder mixture and mixed for another 2-3 min by hand. The powder mixture was directly compressed in single station Tablet punching machine using microcrystalline cellulose as filler and Magnesium stearate as lubricant. The punched tablets weighed about 270 mg (± 20mg) and measured 8 mm in diameter punch. The directly compressed granules were subjected to evaluation as per the methods suggested in Indian Pharmacopoeia like Angle of repose, Bulk density, Compressibility index, Total porosity etc. The angle of repose of granules was determined by the funnel method .The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated. A quantity of 10 g of powder from each formula, previously lightly shaken to break any agglomerates formed. It was introduced into a 50-mL measuring cylinder. After the initial volume was observed, the cylinder was placed in the tap density apparatus. The tapping was continued until no further change in volume was noted. LBD and TBD are calculated by using following formula**.** The crown thickness of individual tablets may be measured with a micrometer. The thickness of the tablets was determined using sliding caliper scale or thickness gauge. Five tablets from each batch were used, and average values were calculated. . Tablets thickness should be controlled within a ± 5 % variation of standard value. The USP weight variation test is run by weighing 20 tablets individually, and the average weight, were calculated from total weight .The individual tablets weight was compared with the average weight. The data was interpreted with the standard. The tablets meet the USP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit. Five tablets were taken in a mortar powdered and mixed well. The 100 mg of powder was weighed and added to a 100 ml of slandered flask and made up to the volume with phosphate buffer pH7.4. The 5 ml was pipetted from the stock solution and made up into 50 ml with phosphate buffer pH7.4, the absorbance of the solution were measured in UV-visible spectroscopy at 280 nm. Hardness of tablets were determined using Monsanto hardness tester. The test consists of a barrel containing a compressible spring held between two plungers. The lower punch is contact with the tablet, surface setting to zero reading. The upper punch plunger is forced against a spring by turning a thread bolt until the tablet fracture. As the spring is compressed, a pointer rides along the gauge in the barrel to indicate the force. The reading is noted down and similar steps are reported to get the average value. For friability test ten tablets were accurately weighed and placed in plastic chamber that rotate at 25 rpm for 4 min, dropping the tablet at a distance of 6 inches with each revolution. The procedure is done which is for 100 revolutions. The tablets were dusted, reweighed and reported**.** Dissolution studies were performed three times and the mean values were taken. Matrix tablets were added to the dissolution medium and experiment was carried out. An equal volume of fresh medium was immediately replaced to maintain the sink condition. The samples were analyzed spectrophotometrically at 280 nm using UV spectrophotometer to assay the amount of Cefuroxime Axetil released at each time interval.

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RESULTS AND DISCUSSION

Matrix tablets of Cefuroxime Axetil were prepared by direct compression and melt granulation method using different matrix material like guar gum, xanthan gum, lanette wax and bees wax

alone/ or in combination with ethyl cellulose. Preformulation studies were carried out on matrix blend and granules. Various parameters like Angle of repose, Bulk density, Tapped density, Compressibility index, Hausner ratio were calculated. Angle of repose was found to be in the range of 25.09^0-36.28^0, which indicates good flow property. The bulk density & Tapped density of all the ingredients was found 0.37 – 0.55 gm/ml and 0.56 – 0.73 gm/ml respectively. This shows good repacking ability of blend. The Compressibility index of the ingredients was found to be in the range of 23.80 – 41.93 & and the Hausner ratio in the range of 1.33 – 1.72. These findings proves that the composition of ingredients for compression posses sufficient flow property and good compression property. Direct compression was used for compressing blends matrix materials like guar gum and xanthan gum. Formulations with bees wax and lanette wax as matrix formers were prepared by melt granulation method. The formulated tablets were subjected to various evaluation tests like Dimension, Hardness, Friability, Weight variation and content uniformity as per standards. Dimensions of all tablets were found to be uniform indicating efficiency of the punching process. Hardness and friability of the tablets was found to be in the range of 5 – 10 Kg/ cm^2 & 0.04 – 0.82 %. Low friability & hardness value confirmed the adequate mechanical strength of the tablets. Weight variation of the tablets was found to be within the specified limit, revealing the reproducibility and suitability of the method used for compression. The content uniformity of all the batches lies within the range of 95-104.25 % w/w clearly proves that uniform distribution of drug in blend and granules. The overall results of the evaluation parameters were found to correlate well with the standards. The % CR from the guar gum matrix tablets was found in the range of 88.15 % -74.49 % CR in 8 h. It was noticed that incorporation of EC in matrix tablets with Guar Gum doesn't have significant effect in sustaining the release from sample .It was also noticed that, on decreasing EC concentration from 15 %-5 %, the release rate tends to increase in the samples from 72.35 % -81.35 %CR in the batches AG5 & AG6 respectively.

. The % CR from the matrix tablets was found to be in the range of 85.74 % - 63.25 %CR in 8 h. It was noticed that incorporation of EC in matrix tablets with Xanthan Gum doesn't have significant effect in sustaining the release from batches .It was also noticed that, on decreasing EC concentration from 15%-5%, the release rate tends to increase in the samples from 68.57 % - 74.56 % CR in the batches AX5&AX6 respectively. The **%** CR from matrix tablets was found to be in the range of 41.28 % - 7.22 % CR in **8** h. It was also noticed that incorporation of EC in matrix tablets with Bees Wax doesn't have significant effect in sustaining the release .It was also noticed that, on decreasing EC concentration from 15% - 5%, the % CR was tends **t**o increase observed from 32.54 % - 38.56 % CR in the batches AB5 & AB6 respectively. . The % CR from the matrix tablets was found to be in the range of 21.73 % -12.76 % CR in 8 h. It was noticed that on adding EC in matrix tablets with Lanette Wax doesn't have significant effect in sustaining the release from the sample .It was also noticed that, on decreasing EC concentration from 15%-5**%** ,the release rate was found to increase from 19.77 % -22.33 % CR in AL5 & AL6 respectively. The release data of all samples were compared .On comparison it was observed that the release tends to decrease with concentration of matrix material used in samples. The interpretation of the data revealed that batches which Guar Gum & Xanthan Gum were found to give a higher release rate from 63.25 % -88.15% CR in 8 hr period than waxy material. The possible reason for such release behavior may be hydrophilicity of the gums used in the samples. The gums would have absorbed the dissolution medium, swelled up and formed a gel like layer around the drug. The drug release must have slowed down due to the high viscous layer of gum based matrix materials. It was also noticed that xanthan gum was more effective than guar gum in slowing down the drug release from samples. The comparison data of samples with Bees Wax & Lanette Wax as matrix materials was performed and it was found that the release rate from the sample with waxy material was found to be % CR, 7.22 % -21.73 % CR

which is less than the samples with gum based matrix materials. This type of slow release may be attributed to high hydrophobicity of waxy material and it would have slowed down the diffusion of dissolution medium in to the core. This phenomenon would have leads to slow diffusion of drug the waxy material. It was also observed that Bees Wax was more effective than sustained release that Lanette Wax. The dissolution data was substituted in various kinetic equations to ascertain the mechanism of drug release from samples. The correlation coefficient value for zero order and Hixson Crowell model was found to be near to 0.99 indicating that the dissolution profile of the samples followed zero order kinetics and Hixson Crowell model. Release data was also fitted in Korsmeyer Peppas equation and the n value was found to be more than 0.45 stating that the release pattern in all formulations follow Non-Fickian transport i.e. drug release is mediated through erosion as well as diffusion.

Figure: 1 *In vitro* release profile of matrix tablets- Guar gum

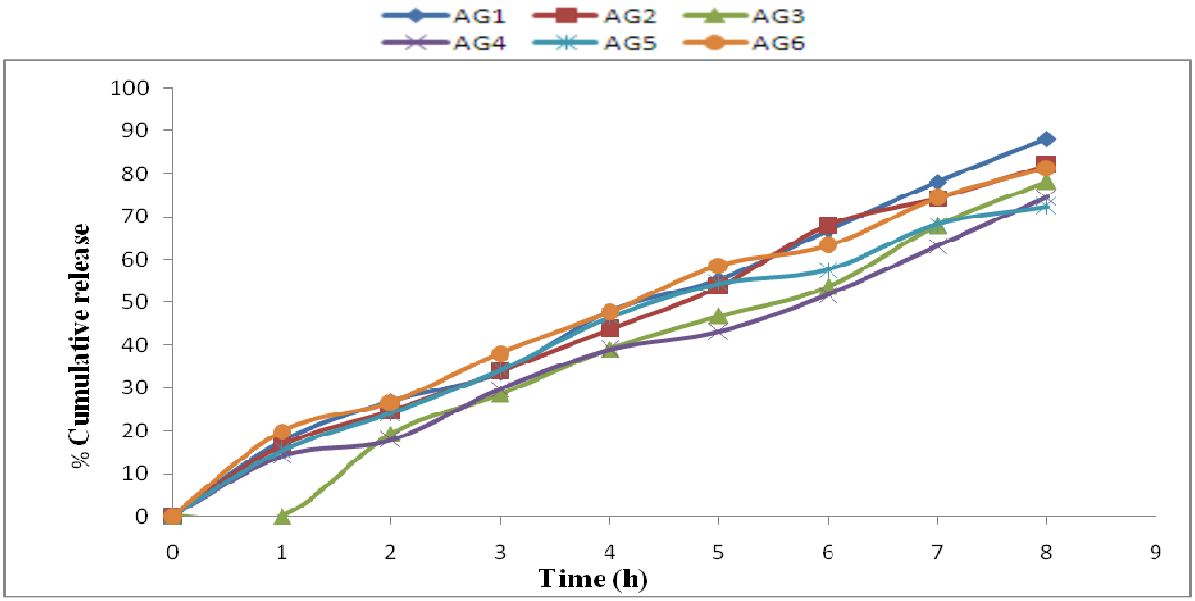

Figure: 2 *In vitro* release profile of matrix tablets- Xanthan gum

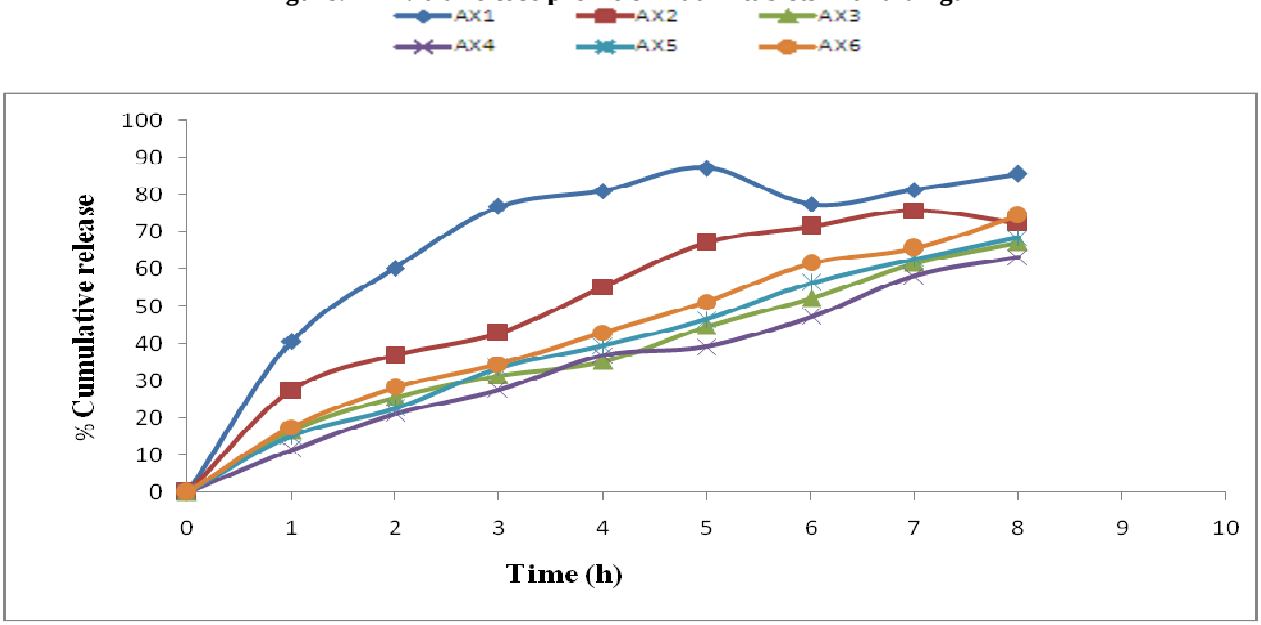

Figure: 3 *In vitro* release profile of matrix tablets- Bees wax

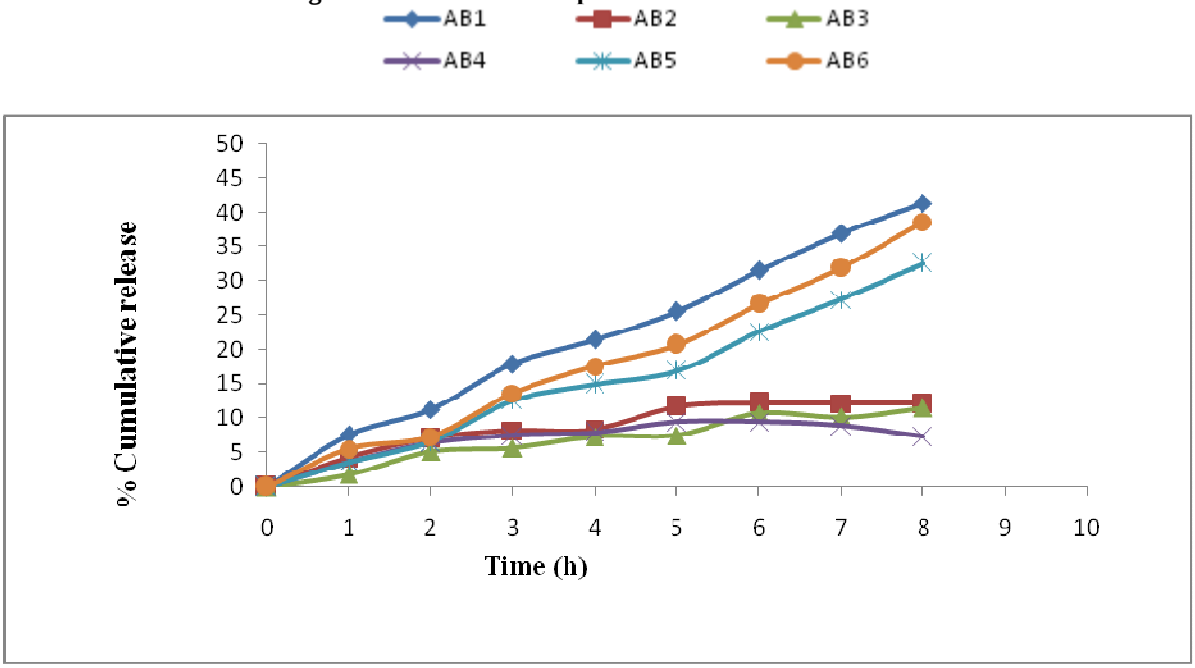

Figure: 4 *In vitro* release profile of matrix tablets- Lanette wax

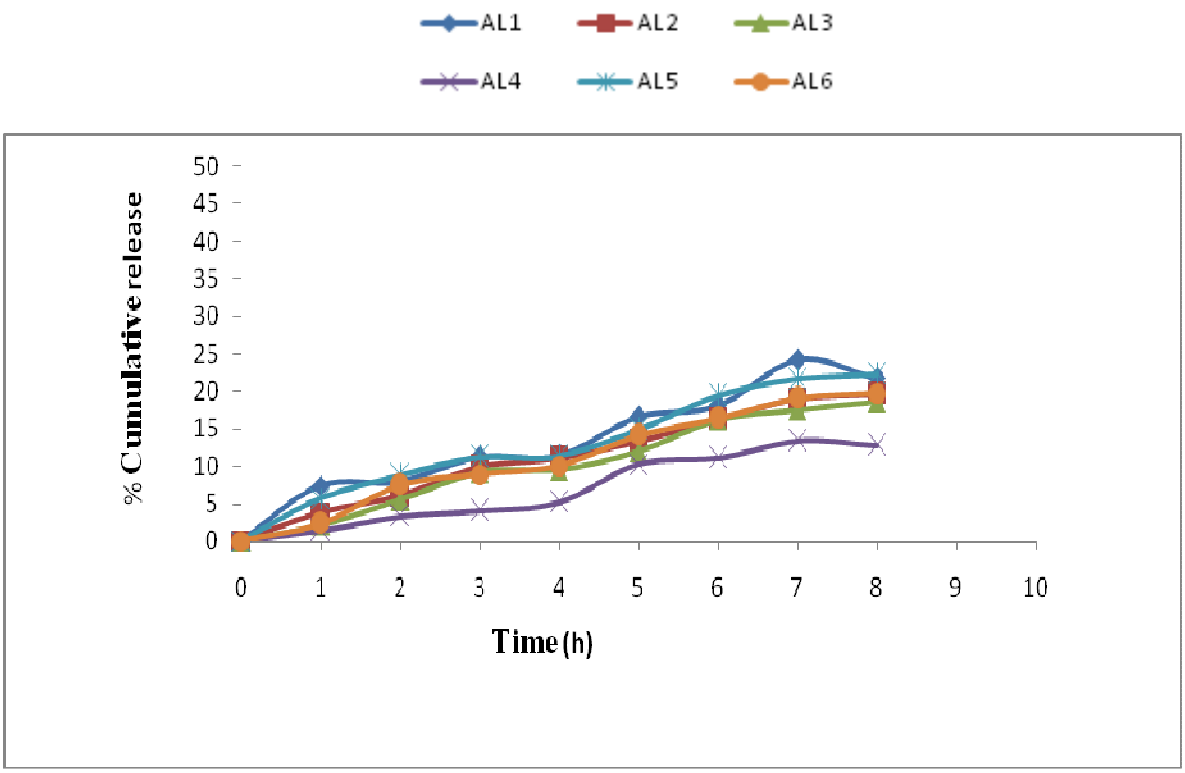

Table: 1 Kinetic evaluation Data of Matrix Tablets - (GM, XG, BW&LW).

Matrix Material	Batch Code (r^2)	Zero Order (r^2)	First Order (r^2)	Higuchi (r^2)	Korsmeyer-peppas		Hixon Crowel (r^2)
					(r^2)	n	
Guar Gum	**AG1**	**0.996**	0.990	0.973	0.918	**0.743**	**0.993**
	AG2	**0.994**	0.961	0.973	0.983	0.771	**0.981**
	AG3	**0.989**	0.924	0.949	0.975	0.782	**0.985**
	AG4	**0.987**	0.931	0.952	0.971	0.811	**0.957**
	AG5	**0.982**	0.989	0.989	0.993	0.769	**0.992**
	AG6	**0.994**	0.967	0.982	0.982	0.680	**0.986**
Xanthan Gum	**AX1**	**0.630**	0.651	0.745	0.699	0.897	**0.654**
	AX2	**0.922**	0.932	0.953	0.966	0.521	**0.932**
	AX3	**0.992**	0.967	0.964	0.976	0.680	**0.979**
	AX4	**0.990**	0.972	0.975	0.987	0.828	**0.982**
	AX5	**0.995**	0.998	0.987	0.993	0.750	**0.995**
	AX6	**0.995**	0.978	0.985	0.995	0.684	**0.990**
Bees Wax	**AB1**	**0.996**	0.991	0.973	0.918	0.861	**0.993**
	AB2	**0.872**	0.875	0.923	0.594	0.907	**0.872**
	AB3	**0.931**	0.934	0.953	0.698	0.781	**0.933**
	AB4	**0.472**	0.471	0.598	0.518	0.890	**0.472**
	AB5	**0.985**	0.975	0.953	0.904	0.862	**0.979**
	AB6	**0.987**	0.973	0.945	0.898	0.971	**0.979**
Lanette Wax	**AL1**	**0.926**	0.917	0.889	0.683	0.912	**0.981**
	AL2	**0.987**	0.989	0.983	0.787	0.982	**0.988**
	AL3	**0.973**	0.976	0.976	0.840	0.978	**0.975**
	AL4	**0.939**	0.938	0.922	0.804	0.823	**0.938**
	AL5	**0.971**	0.969	0.947	0.733	0.857	**0.969**
	AL6	**0.974**	0.977	0.976	0.834	0.927	**0.976**

CONCLUSION

Preformulation parameters of matrix blend and granules were found to be within the standard limit. Post compression parameters were found to comply with the standards. Release study results showed that wax based materials were able to sustain the release much better than gum based matrix formers. Xanthan gum was found to be more effective than Guar gum- among gum based matrix formers. Lanette wax was found to be more effective than Bees wax –among waxy matrix materials. The release rate tends to decrease with the concentration of all matrix materials used for formulations. There was no significant effect due to incorporation of EC in samples; Release model of sample was found to be zero and Hixson Crowell model with high linearity. Mechanism of release from samples was found to be Non- Fickion in nature.

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