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APPLICATION OF QUALITY BY DESIGN (QBD) IN FORMULATION DEVELOPMENT OF IMMEDIATE AND EXTENDED RELEASE BILAYERED TABLETS OF DEXTROMETHORPHAN AS A MODEL DRUG

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ABSTRACT:

Quality by Design (QbD) is an approach in the design and development of the formulation by using different scientific strategies, tools and previous data available. QbD can assist the pharmaceutical industry and research scholars to satisfactorily move towards the more scientific, active, risk-based pharmaceutical development. Qbd, if applied, to the entire product cycle minimizes the end product testings and leaves one with safe, effective and quality product.

In the present study, an attempt is made to apply the QbD to the Dextromethorphan, a highly potent opiod analgesic and antitussive drug which have relatively lesser addictive and narcotic properties. It is designed in immediate and extended release manner for better therapeutic efficacy. Due to the shorter half life of Dextromethorphan it needs to be taken four to five times a day. To reduce the frequency of dose it can be formulated in extended release form by wet granulation method.

The tablets were prepared by direct compression of matrix-type immediate release layer and ethyl cellulose coated extended release layer in bilayered rotary press (Remik, Mini Press II DL). Physical mixture of drug and the excepients is found to be compatible when evaluated using FTIR and the tablets are evaluated for hardness, thickness, weight variation, friability, content uniformity, distintegration and dissolution profile. The effect of Binder, superdistintegrant and coating concentrations are also optimized by using the design space and other plots with the help of Minitabs Software version 17.

The prepared formulation showed better dissolution profiles than the available products.

Keywords: *Dextromethorphan HBr, Quality by Design, Extended Release, Antitussive, Minitabs Version 17*

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INTRODUCTION

Quality by Design – Principles & Elements:

Quality is the driving force for every pharmaceutical company to run and comply with the patients needs and requirements satisfactorily. Either it is product, process or service quality is required [1,2].

Quality by design (QbD) is an intelligent approach to built quality in products and process. This can be achieved by constructive planning and the previous data available. Although it is based on risks, but it has its fruits that it minimises the end product testings and increases the chances of regulatory acceptance. QbD was first proposed by a well known researcher Joseph Moses Juran. Later it has been accepted by ICH, US-FDA and other regulatory bodies. The principles of QbD is best explained by ICH Q8, ICH Q9 & ICH Q10, which gives the guidelines on Science & Risk-based assessment, product's life cycle and its approach, and the various method designs. US-FDA also highlights the key role of QbD in Process Analytical Technology (PAT) which is nothing but a Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance [3,4,5].

The various advantages of QbD include the patient's safety and satisfaction, core understanding of any pharmaceutical process and its design and development in a better way. Apart from this, other business benefits and reduced expenditure on PAC (Post Approval Changes).

The elements of QbD include:

- New objective design
- Critical quality attributes determination and their assessment
- Assessment of Risk
- Development of experimental design
- Implementation of designed-Control Strategy and
- Continuous improvement

Extended Release Systems:

Extended release systems are designed in such a way so as to extend the release of drug from the dosage form thus retaining it in the systemic circulation for longer period of time and prolonging the action[6,7,8].

MATERIALS AND METHODS

Materials: Dextromethorphan HBr was obtained from Dr Reddy's Lab., Hyderabad, Mannitol, HPMC, Guar gum from S.D. Fine Chemicals Ltd, Mumbai. Ethyl Cellulose from Corel Pharmaceuticals, Ahmedabad, India. Other chemicals are analytical grade.

Software:

Minitabs Software version 17

Method:

The bilayered tablets of Dextromethorphan are manufactured in the following manner.

1. The immediate layered is prepared by direct compression method
2. The extended release layer is prepared by wet granulation method.

Manufacturing Process for Immediate release Layer:

The corresponding amounts of DXM HBr, SSG, Guar gum and mannitol are weighed and the powders were sieved using screen #25 and triturated. Magnesium stearate and talc are added just before the compression.

Manufacturing Process for Extended release Layer:

The corresponding amounts of DXM HBr, HPMC, Guar gum and mannitol are weighed and powders were sieved using screen #25. Ethanolic EC is now poured onto the screened powder and kneaded properly to form the lump. The lump is now passed through sieve #100 to get the wet granules. The wet granules are dried using Hot Air Oven. Magnesium stearate and talc are added just before the compression.

The layers are separately weighed and punched using Rimek, Mini press-II DL Rotary Press. Tablets were collected during compression for in-process testing (weight variation and Hardness)

Formulation:

The different formulations prepared in this study are as follows:

Table 1: Composition of Immediate release and Extended Release Layer

	F1	F2	F3	F4
Immediate Release Layer				
Dextromethorphan(mg)	5	5	5	5
Guar Gum(mg)	0.5	0.6	0.7	0.8
SodiumStarch Glycolate(mg)	1	1.5	2	2.5
Magnesium Stearate(mg)	0.5	0.5	0.5	0.5
Talc(mg)	0.3	0.3	0.3	0.3
Mannitol(mg)	30.2	29.6	29	28.4
Extended Release Layer				
Dextromethorphan(mg)	5	5	5	5
Ethyl Cellulose(mg)	0.18	0.23	0.26	0.3
HPMC(mg)	0.4	0.8	1.2	1.6
Guar Gum(mg)	0.5	0.6	0.7	0.8
Magnesium stearate(mg)	0.5	0.5	0.5	0.5
Talc(mg)	0.3	0.3	0.3	0.3
Mannitol(mg)	30.62	30.07	29.54	29

Dissolution Studies:

In vitro drug release was performed for the manufactured tablets according to the USP 26, over a 8-hour period, using a paddle dissolution system. A minimum of 6 tablets per batch were tested. The USP paddle method was used at 100 rpm. The media used was 0.1N HCl at a pH 2.0 and a volume of 750 ml for the first 2 hours after which 250 ml of 0.2M sodium phosphate, tribasic, was added to give a final pH of 6.8 and maintained at 37+ 0.5^{o}C.

Dextromethorphan release from each tablet (in the dissolution samples) was determined by UV double beam Spectrometer at 278nm.

Predicting Mechanism of drug release

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data was fitted in to zero order, first order, higuchi and Korsmeyer-Peppas release model, to study the drug release from the dosage form

Zero order release rate kinetics:

To study the zero—order release kinetics the release data are fitted to the following equation.

$$F=K_o.t$$

Where 'F' is the drug release, 'K' is the release rate constant and 't' is the release time. The plot of %drug release versus time is linear.

First order release kinetics:

The release rate data are fitted to the following equation.

$$Log\ (100-F) = kt$$

A plot of log % drug release versus time is linear.

Higuchi release model:

To study the Higuchi release kinetics, the release rate data were fitted to the following equation,

$$F= k\ t^{1/2}$$

Where 'k' is the Higuchi constant

In Higuchi model, a plot of % release versus square root of time is linear.

Korsemeyer and Peppas release model:

The release rate data were fitted into the following equation,

$$M_t / M_\alpha = K.t^n$$

Where M_t / M_α is the fraction of drug released,

'K' is the release constant,

't ' is the release time.

'n' is diffusion exponent, if n is equal to 0.89 the release is zero order, if n=0.45 the release is best explained by Fickian diffusion, and if 0.45<n<0.89 then the release through anomalous diffusion or non-fickian diffusion (Swellable and Cylindrical matrix).

In this model a plot of log (M_t / M_α) versus log (time) is linear.

Creation of Design Space:

Design space is created in the 3D sheets by using Minitabs version 17 to optimize the superdisintegrant, concentration of coating material and the binder

RESULTS & DISCUSSIONS

Pre-compression Parameters:

The blends of different formulations were evaluated for bulk density and tapped density. The results were shown in above table. The bulk density and tapped density for all the formulations from 0.371 to 0.380 and 0.483 to 0.873 respectively.The values obtained were within the acceptable range and there was no large difference noticed. With this result we can calculate the % compressibility of the powder and Hausner ratio. The percentage compressibility of powder was determined using Carr□s index. Compressibility index lies within the acceptable range of 9.71 to 13.18. Indirectly it is showing that all the blends having good flow properties.

The angle of repose values found to be in the range of 24.50 to 26.10. All the formulations showed angle of repose below 30° which indicated good flow properties of the blends all the results were shown in table 2.

Post Compressional parameters:

Uniformity of weight of all the formulations was done by taking twenty tablets were randomly selected from each formulation andevaluated. The average weight of each formulation was shown in the above table. The values are almost uniform and were within the USP specifications. The weights of the tablets ranged from 73.26 ±0.75mg to 74.88 ±0.64mg. Thus all the formulations passed the test for weight variation. The thickness of the tablets was determined using a calibrated dial caliper. Tablet mean thickness is almost uniform in all the formulations and the values obtained are from 0.752 ±0.01 to 0.58 ±0.02 mm. the standard deviation values indicated that all the formulations werewithin the range with uniform thickness. The values of hardness for tablets are ranged from 2.92 ±0.18 to 3.42 ±0.17. The lower values of standard deviation indicates that the hardness of all the formulations were almost uniform and possess good mechanical strength with sufficient hardness. The friability of tablets were mentioned in above table. The values ranged from 0.40 to 0.69. All the values are below 1% indicates that the tablets of all the formulations are having good withstanding property, the disintegration time was shown 1-3 minutes, all the results were shown in table 3 & 4.

Drug Release:

The in vitro study was carried out using USP dissolution apparatus II (paddle type) .From the dissolution profile of all the formulations (F1-F4), it was found that the formulations F1,F2,F3 and F4 showed drug release up to 8 hrs 99.00%, 88.54%, 93.64% and 96.90% respectively and results were shown in table 5 and figure 1.

Drug Release Kinetics:

The release profile of dextromethorphan of all formulations were compared with zero order, first order, higuchi model and korsemeyer –Peppas model in the figure 2. The data were processed for regression analysis. The data was evaluated for zero order, first order, higuchi model and korsemeyer – Peppas model,the R2 values obtained.

Table 2 Pre-compression parameters

Formulatio code	Blend Property				
	B.D(gm/ml)	T.D(gm/ml)	C.I (%)	H.R	Angle Of Re
F1	0.380	0.500	10.91	1.310	26.1^0
F2	0.710	0.873	09.71	1.251	25.4^0
F3	0.710	0.873	12.74	1.251	24.5^0
F4	0.371	0.483	13.18	1.299	25.1^0

Table 3 Comparative Post-compression Parameters

Formulation Code	Thickness (cm)	Hardness (kg/cm^2)	Wt. Variation (mg)	Friability (%)	Drug Content (%)
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD
F1	0.575±0.020	2.9±0.292	74.875±2.99	0.6 ± 0.04	97.4±2.3
F2	0.579±0.019	2.92±0.109	'3.26±2.54	0.40 ± 0.02	98.2±0.16
F3	0.58±0.017	3.0±0.07	74.32±1.26	0.16 ± 0.02	99.6±1.27
F4	0.572±0.021	3.42±0.25	'4.88±2.87	0.27 ± 0.03	98.9±0.26

Table 4 Concentration of superdisintegrant used and Disintegration Time

Formulation code	Concentration of Superdisintegrant	Disintegration Time
F1	1.33%	**1min 31sec**
F2	2%	**1min 50sec**
F3	2.16%	**2min 10sec**
F4	**3.33%**	**2min 54sec**

Table 5: Comparative Drug release from different formulations

Time (min)	Cumulative drug release (%)	Cumulative drug release (%)	Cumulative drug release (%)	Cumulative drug release (%)
	F1	**F2**	**F3**	**F4**
0	0	0	0	**0**
10	10.65	10.05	10.45	**9.33**
30	29.77	24.34	28.31	**24.68**
45	56.63	51.60	55	**48.43**
60	**77.47**	**70.72**	**71.98**	**65.70**
90	90.63	80.64	82.76	**75.75**
120	92.15	82.02	84.01	**77.27**
180	93.14	83	85	**78.19**
240	95.25	84.79	86.85	**79.64**
300	96.63	86.04	88.3	**81.42**
360	97.42	86.76	90.61	**83.8**
420	98.41	87.62	91.53	**84.59**
480	**99**	**88.54**	**93.64**	**86.90**

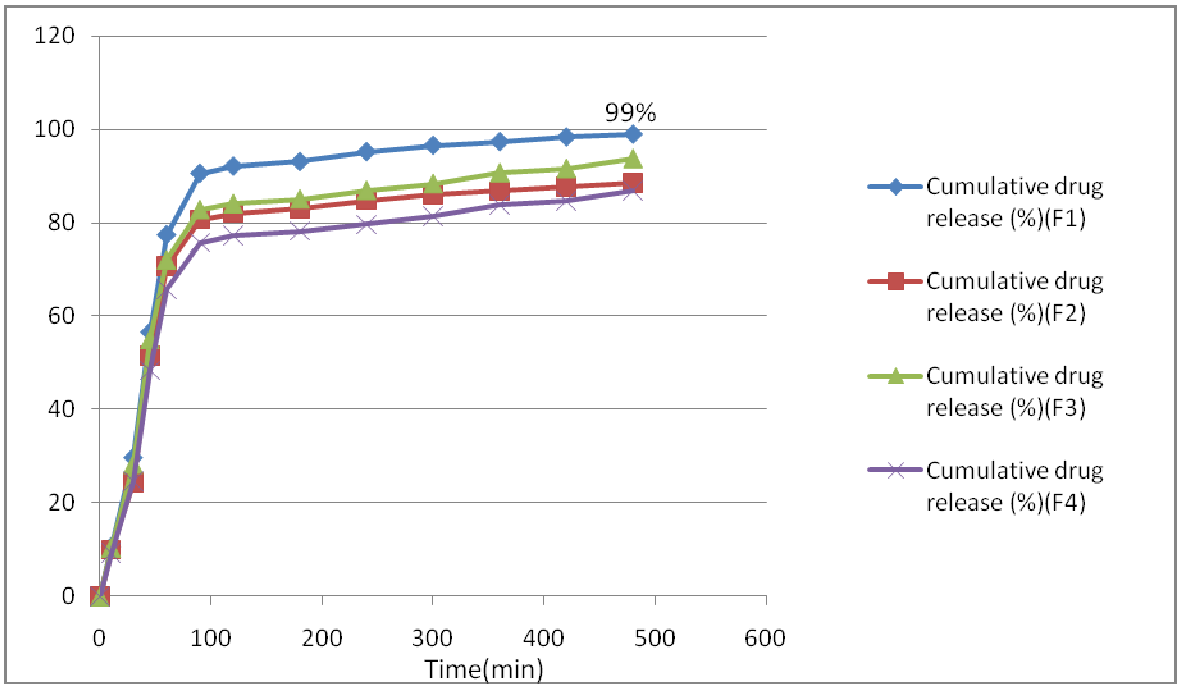

Fig1 Comparative Drug release from different formulations

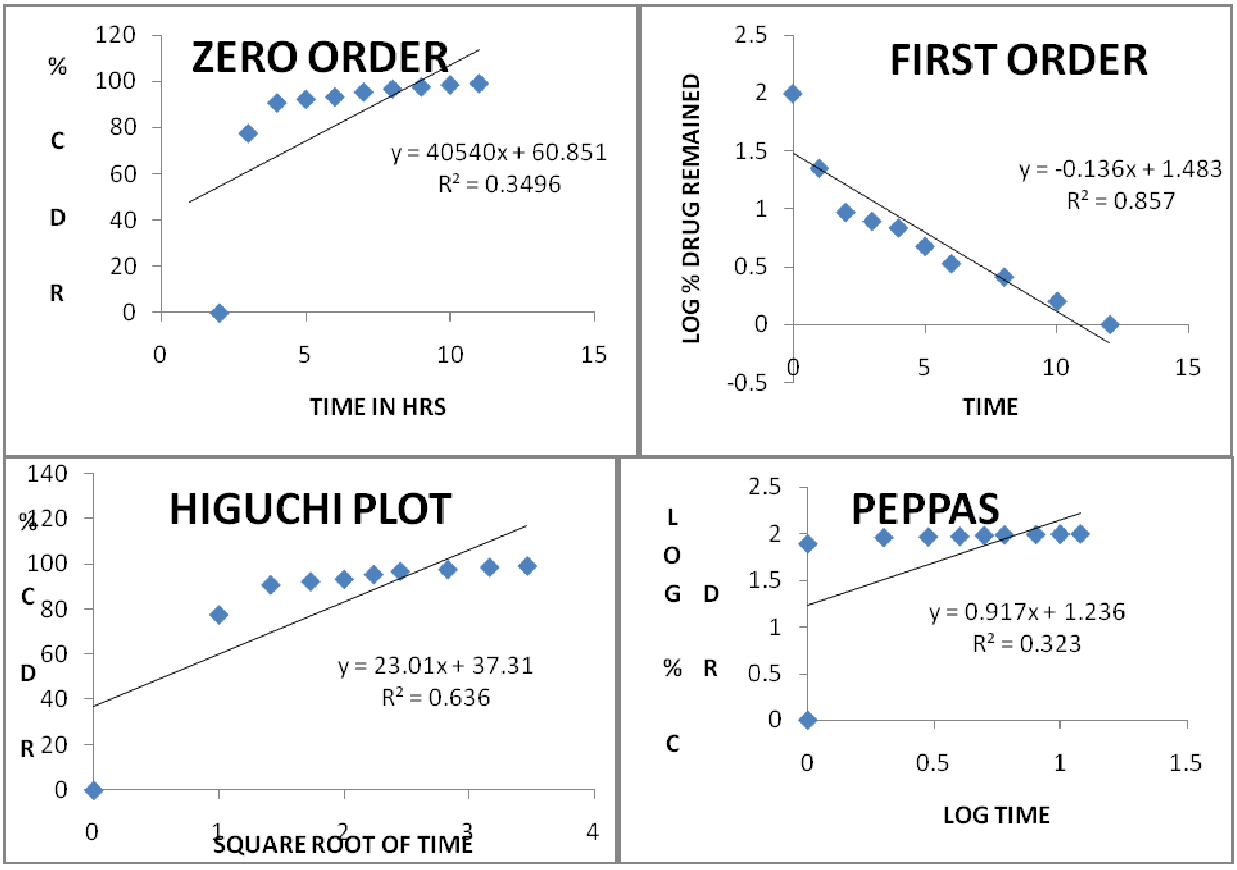

Fig 2: Zero order, First order, Higuchi and Peppas model graph of F1

Design Space:

Design Space for Super-disintegrant (Sodium starch glycolate) and the percentage release at the end of 60min: Sodium starch glycolate(Super-disintegrant) is used in different concentrations in different formulations in immediate release layer. Sodim starch glycolate helps in the release of drug from the formulation in immediate manner.

When the different concentrations of SSG are plotted against the percentage release at the end of 60min the ideal concentration is known from the plot.

Design Space for concentration of coating material (Ethyl cellulose) and the percentage release at the end of 120min:

Discussions:

Ethyl cellulose is used as a coating material. It ensures the release of drug from the extended-release layer in extended pattern.

When the different concentrations of EC are plotted against the percentage release at the end of 120min the ideal concentration is known from the plot.

Design Space for concentration of binder (Guar gum) and the mean hardness: Guar-gum is used as a binder in both the layers in all the formulations. It gives the best hardness to the formulation.

When the different concentrations of Guar gum used, is plotted against the mean hardness the ideal concentration of the binder is known from the plot.

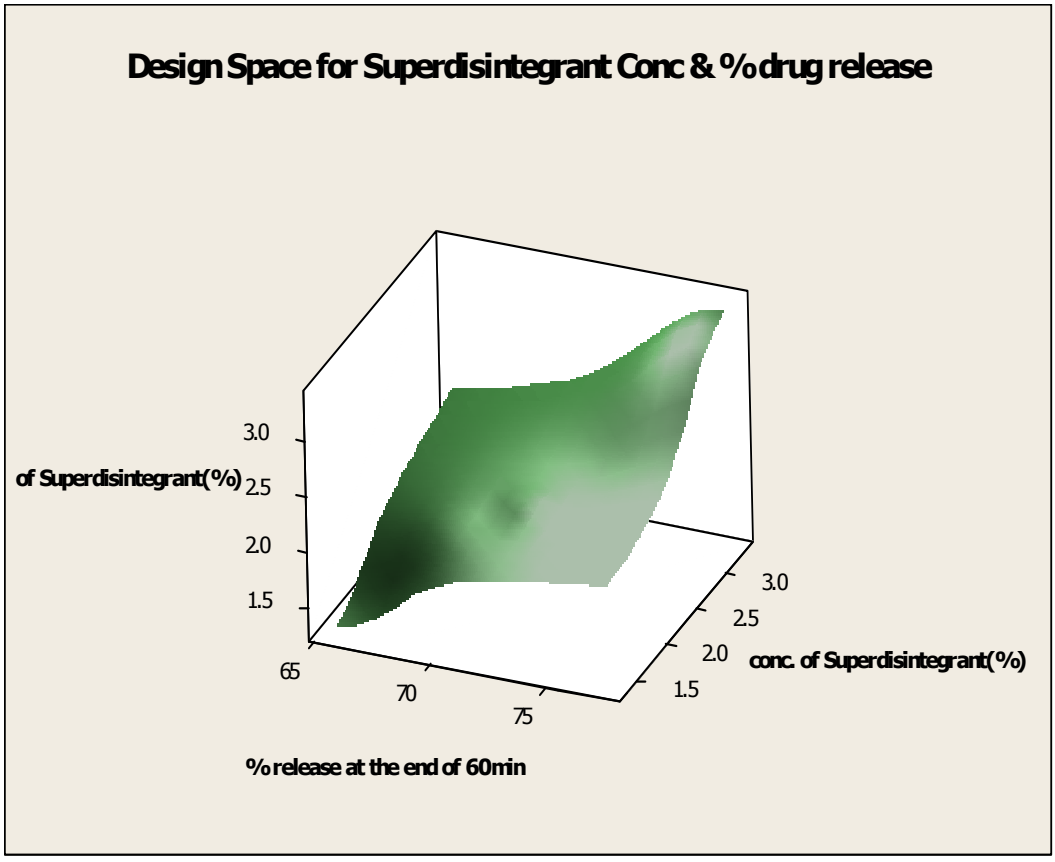

Fig 3: Design Space for Super-disintegrant (Sodium starch glycolate) and the percentage release at the end of 60min

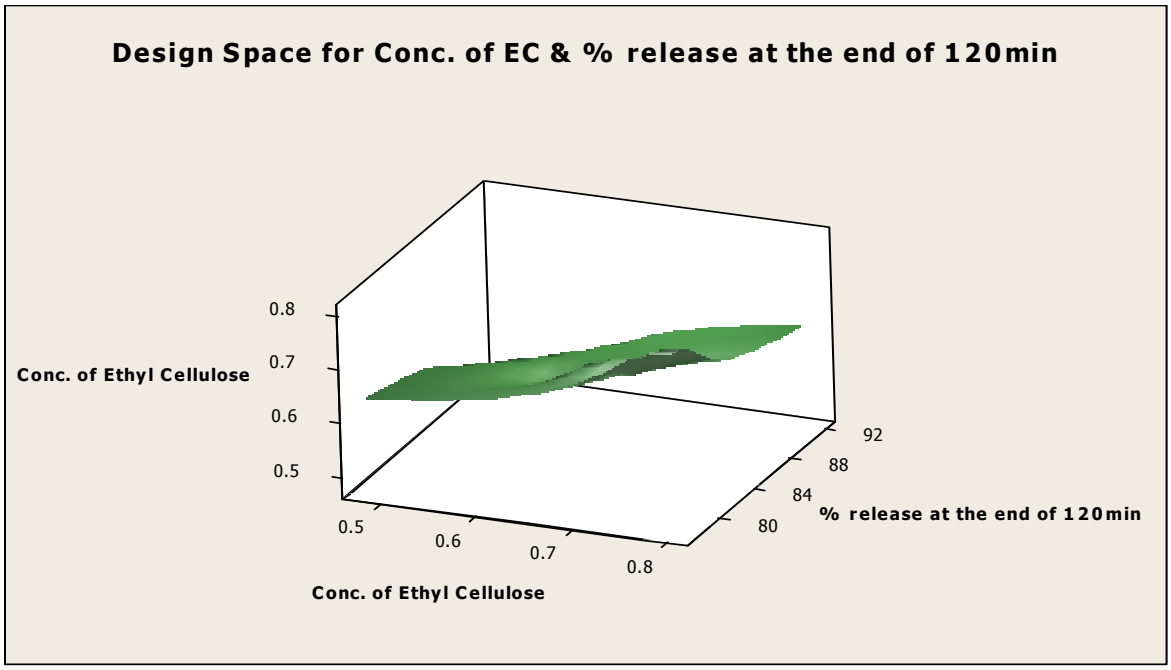

Fig 4: Design Space for concentration of coating material (%) (Ethyl cellulose) and the percentage release at the end of 120min from the different formulations

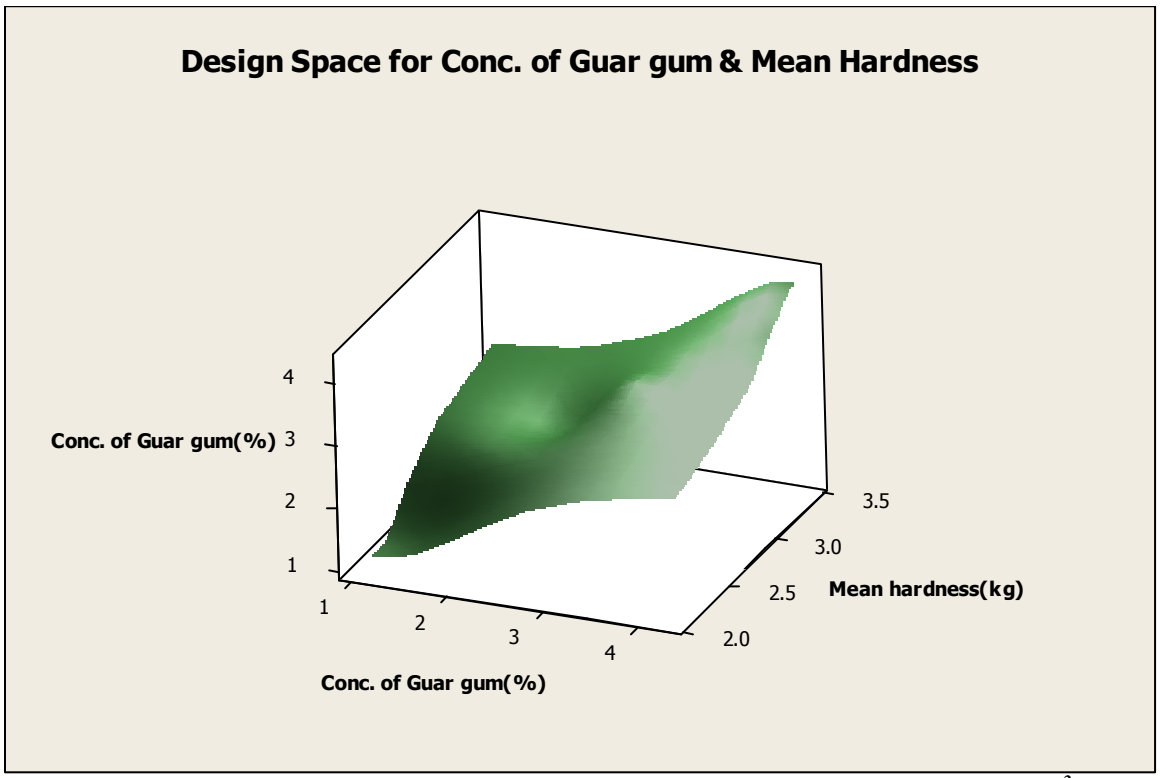

Fig 5: Design Space for concentration of binder (Guar gum) and the mean hardness (kg/cm^2) of different formulations

CONCLUSION:

In the present study attempts were made to prepare immediate and extended release bilayered tablets of Dextromethorphan by using QbD where Dextromethorphan is used both in immediate release layer and extended release layer.

Due it the shorter half life of Dextromethorphan it needs to be taken four to five times a day. To reduce the frequency of dose it can be formulated in extended release form.

Extended release layer was prepared by wet granulation technique using Ethyl cellulose and HPMC, as release retarding polymer and evaluating the parameters like flow properties, physical evaluation such as hardness, weight variation, friability, drug content, *In vitro* drug release. Formulation containing variable such as, different drug: polymer ratios were prepared and treated for different kinetic models of drug release. Immediate release powder and extended release granules showed good flow properties

The prepared bilayer tablets showed hardnes,

friability, drug content values within the limits.

The extended release layer showed decreased release as the concentration of the polymer increases there by it retards the drug release. The drug release from the formulations followed first order kinetics; the correlation coefficient revealed that the First order Kinetic model was applicable to the release data. The values of release exponents 'n' for formulations F_1, F_2 , F_3 and F_4 was below one indicating the release governed by non-Fickian anomalous transport.

The in vitro release data obtained from Formulations was fitted to kinetic models such as zero order, first order, Higuchi and Korsmeyer-Peppas models to explore the release mechanism. The data obtained from the release kinetics fitted with Higuchi model indicated that the release of drug from the tablets was depend on the square root of time. Further, it is important to note that a linear relationship was obtained for a plot of release profile verses time, and the regression coefficient was very close to zero for all the four formulations. The n values obtained from the Korsmeyer-Peppas model showed that the release mechanism was non-Fickian.

Generally, tablets prepared with hydrophilic polymers show a release mechanism of Fickian indicating the passage of drug through the polymer matrix by diffusion.

Optimised formulation was studied for FTIR and it was found to be compatible due to there is no change in shift of main peaks of drug.

In future, a researcher can perform drug safety studies on animal models, comparative studies with the marketed formulation and bioequivalence studies may also be performed as the proposed work.

REFERENCES

1. Artham et al., IJPSR, 2013; Vol. 4(10): 3976-3991
2. Ash, M, Ash, I., 1995. Handbook of Pharmaceutical Additives, Gower Publishing Limited.
3. Ashish Vishwakarma et al, 2012
4. Bain, J. C., Tan, S. B., Ganderton, D. and Solomon, M. C., 1991 Comparison of the in vitro release characteristics of a wax matrix and a hydrogel sustained release diclofenac sodium tablet. Drug Dev., Ind. Pharm. 17 (2): pp 215-232.
5. BASF, 1999. Technical information for Kollidon® SR, BASF AG, Ludwigshafen/Rh., Germany.
6. Bem J. L., and Peck R., 1992 Dextromethorphan: an overview of safety issues. Drug Safety; 7:190-199.
7. Bharaj, S. S., Takka, S., Kelm, G.R., Sakr, A., 2005. Development and in vivo evaluation of extended release dextromethorphan tablets, Part 1, Accepted for publication in Pharm. Ind. 67
8. Bharaj, S. S., Takka, S., Kelm, G.R., Sakr, A., 2005. Development and in vivo evaluation of extended release dextromethorphan tablets, Part 2, accepted for publication in Pharm. Ind.