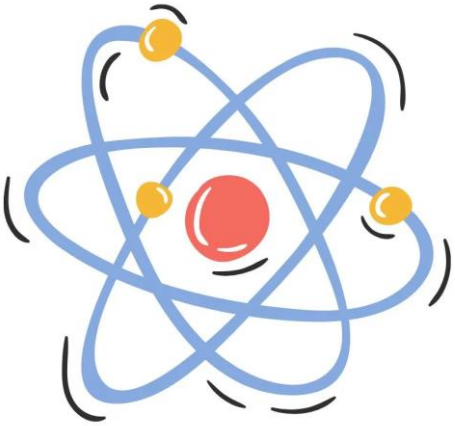

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ASSESSMENT OF BENECEL™ HYPROMELLOSE GRADES IN THE DEVELOPMENT OF SUSTAIN RELEASE GABAPENTIN TABLETS

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ABSTRACT - *Purpose:* The purpose of this work was to assess the impact of Benecel DC grades on gabapentin product development. Commercial Gabapentin tablets are manufactured using a high-shear granulation and fluid-bed granulation process, but this process has several disadvantages like increasing the complexity of the process and increasing the manufacturing cycle time. To avoid a granulation step completely, direct compression is a suitable method for the formulation of sustained release gabapentin tablets. *Methods:* The tablets were prepared by direct compression method along with hydrophilic matrix materials like Benecel K4 PH DC, Benecel K15 PH DC and Benecel K100 PH DC. The blends were evaluated for DSC analysis, FTIR analysis, bulk density, angle of repose, and compressibility index. The tablets were subjected to thickness, diameter, weight variation test, drug content, hardness, friability, kinetic model and in vitro release studies. *Results:* The preformulation results suggested that the benecel grades are suitable as DC material. The results of the FTIR & DSC study showed that there was no interaction between Gabapentin & Benecel K5, Benecel K15, Benecel K100. The in-vitro dissolution study, kinetic model, drug content, swelling index, and stability studies showed good results. *Conclusion:* According to the industry perspective, the benecel DC grade should provide better performance in direct compression applications than standard grades of HPMC, as well as reduce process complexity, low cost, and manufacturing cycle time.

KEYWORDS - Gabapentin, Benecel DC Grades, Matrix tablet, Direct compression method.

Introduction:

The oral route of administration of medication has received the most attention because it is simple, convenient, and safer. [1] The conventional release/immediate-release tablets have a rapid onset of action and are eliminated from the body once they reach the Maximum Plasma Concentration and thus have shorter duration of action. Controlled-release tablets are used to provide a long duration of action with a minimal adverse effects. [2] To achieve sustained API release, they are formulated with a natural high-intensity polymer. [3] Gabapentin-controlled release tablets are often prescribed for chronic, severe neuronal pain caused by certain long-term diseases. [4]

Gabapentin is commonly used as an analgesic and an anticonvulsant agent. [5] Gabapentin is classified as a Class III drug by the biopharmaceutical classification system (BCS). The usual dose for epilepsy is 0.9–3.6 g daily, but it can be increased to 1.8 g daily for neuropathic pain. [6] Gabapentin has poor mechanical properties and a high load of 800 mg per tablet. Gabapentin has low tablet tensile strength, tablet capping, and tablet speed sensitivity. Commercial GABA tablets are produced using a high-shear or fluid-bed granulation process, but this has several drawbacks, including increased process complexity and manufacturing cycle time. [7]

Thermal treatment and milling show an interconversion between polymorphic forms. According to studies, the lactamization rate increased when the milling time was increased. Lactimization rates in gabapentin samples milled for 60 minutes were 500 times higher than in non-milled samples. Furthermore, higher rates of lactamization in milled samples were associated with increasing surface area, milling time, and lactam levels during manufacture. The most startling results are from the rate of lactamization in milled samples exposed to different degrees of ambient humidity at 50°C. The lactamization rate was greatest in the presence of the lowest humidity conditions and decreased dramatically as humidity increased. [8]

Previously, four crystal forms (I-IV) were reported, with form I being a monohydrate and forms II-IV of been anhydrases. Under ambient conditions, Form II is the most stable anhydrous form and is used in the current study. [9] Form III is metastable, while Form IV has not been thoroughly studied. [10]Gastroretentive delivery systems are primarily intended for drugs with a narrow absorption window, a biological half-life of 2–8 hours and drugs are taken in multiple daily doses, which allows for the development of controlled-release talets. Controlled-release tablets will aid in reducing dose dependence. A prolonged release allows for slower absorptionof the drug, offering advantages over immediate release by reducing themaximum concentration of the drug (Cmax) thereby reducing adverseside effects associated with high blood concentrations. Additionally, by extending times between doses it can also lead to improved patient compliance to dosing schedules resulting in improved overall efficacy.[11]

HPMC has benefited from recent advances in the availability of several directly compressible (DC) grades for use in the formulation of controlled-release matrix tablets. To improve flow and compressibility, the Benecel DC grades are co-processed with silica at < 1% wt. A directly compressible version of hydroxypropyl methylcellulose allows the drug to be mixed directly with the excipients, thus eliminating the need for a granulation step. Not only does this reduce manufacturing equipment and cycle times, but also reduces the amount of drug (active pharmaceutical ingredient) required as well as the development work required to establish the process parameters, design space, and scale of granulation processes because there are fewer process steps to characterize and optimize. This reduces development costs and time, allowing important medicine to reach patients faster. Currently the three are available as DC grades. These grades represent a range of viscosities that can be used for controlled released hydrophilic matrix tablets.[12]

Table 1:Viscosity of different grades of Benecel

Grade	**Solution concentration**	**Viscosity (mPa-^{s} ^{a})**
Benecel K4M PH DC	2%	80-120
Benecel K15M PH DC	2%	200-300
Benecel K100M PH DC	2%	562-1050

With improved flow of the Benecel DC grades these formulations may be feasible to avoid the granulation step and use the material in a direct compression process. This has the advantage of reducing the complexity of the process and decreasing the manufacturing cycle time.

The main objective of this study is to resolve the manufacturing hurdles of gabapentin tablets, and the core objective is to eliminate solid-state transformations of gabapentin form II and lactamization rates caused by the thermal treatment, milling, and co-milling process. Benecel's recent DC grades, such as Benecel K100M PH DC, Benecel K15M PH DC, and Benecel K4M PH DC, have attracted the attention of research scientists and are intended to explore and optimize the variables and mechanical properties of the controlled release tablets.

Materials:

Gabapentin was provided as gift sample by Intas pharmaceuticals limited, Benecel K4M PH DC, Benecel K15M PH DC, Benecel K100M PH DC, the polymer obtained by Ashland , HPMC K 100, Microcrystalline cellulose PH 102, Talc powder, Magnesium stearate were purchased from Loba chemical pvt ltd,Mumbai. All the chemicals and solvents used were of Analytical grade.

Method:

Preparation of tablets: The direct compression technique is used to create this formulation. Gabapentin, Benecel DC grade, and all ingredients were mixed and passed through 60#seive in each formulation. All the ingredients were thoroughly combined by triturating for up to 15 minutes. The powder mixture was lubricated, and tablets were prepared by using the direct compression method. [13]

Table 2:Gabapentin tablets

INGREDIENTS	BK4	BK15	BK100	HK100
Gabapentin	450 mg	450 mg	450 mg	450 mg
Benecel K4M PH DC	100 mg	-	-	-
Benecel K15M PH DC	-	100 mg	-	-
Benecel K100M PH DC	-	-	100 mg	-
HPMC K100	-	-	-	100 mg
Microcrystalline cellulose PH 102	37 mg	37 mg	37 mg	37 mg
TALC Powder	6.5 mg	6.5 mg	6.5 mg	6.5 mg
Magnesium stearate	6.5 mg	6.5 mg	6.5 mg	6.5 mg
Total weight	600 mg	600 mg	600 mg	600 mg

PREFORMULATION STUDIES:

Angle of repose: The angle of repose can be used to calculate the frictional forces in loose powder or granules. Angle of repose was determined by using funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel is fixed and just touches the heap of the blends. Accurately weighed blend is allowed to pass through the funnel freely on the surface. The angle of repose was calculated using heigt(h) and radius(r) of the pile[14].

Bulk density, tapped density and Compressibility:

The bulk and tapped volume were determined according to Ph. Eur. 9th Ed. (2.9.34. Bulk density and tapped density of powders) by gently introducing accurately weighed amount of sample into dry, graduated 100-mL glass cylinder. Then the sample was mechanically tapped 100 times using a tapped density tester to determine tapped volume. The bulk and tapped density in grams per millilitre were calculated from the ratio of the mass and volume of the sample. All determinations were made in triplicate.

The compressibility Index and Hausner's Ratio are measures of the proclivity of a powder to be compressed. As such, they serve as an indication of the relative importance of inter particulate interaction. In a free-flowing power system, such interactions are generally less common, and tapped densities are more similar in value. In poorer flowing materials, there are frequently greater inter-particle interactions and a greater difference between bulk and tapped densities will be observed resulting in higher values of compressibility index and Hausner's ratio. [15]

FOURIER TRANSFORMS INFRARED SPECTROMETRY (FTIR):

The FTIR study's purpose was to provide qualitative and quantitative analysis for detecting chemical bonds or functional groups on the drug surface, as well as excipients.The FTIR spectra of pure drug and its physical mixture with polymers were performed. On the basis of physical observation, suspending agents, preservatives, and surfactants were selected for further FTIR study. Instead of NaCl, this KBr pellet approach is used because it has a selective advantage in that it produces measurement results in the 4000 – 400 cm-1 range, whereas NaCl produces results in the 4000 – 600 cm-1. Several functional groups at different IR ranges, when compared to the standard drug FTIR graph. [16]

DSC Method (Differential Scanning Calorimetry):

DSC measures a system's heat capacity as a function of temperature. Following the changes in the sample's heat capacity as a function of temperature, phase transitions of various orders can be detected. DSC of pure durg and physical mixture of drug and polymer was carried out.Thermal analysis was carried out using a differential scanning calorimeter (Mettler Toledo DSC 822e). Samples were placed in aluminium pans and crimped with an aluminium lid. The heating rate was 10 ˚C/min in the range of 25–250 ˚C, in a nitrogen flow of 50 ml /min was utilized as punging agent. [17]

XRD:

Samples werefilled in a glass holder and exposed to Cu Kα radiation(45 kV×40 mA) in a wide angle X-ray diffractometer at ambient temperature. X-ray diffraction (XRD) analysis was carried out using Cu Kα radiation (λ = 0.1540 nm, a tube operated at 40 kV and a filament current of 40 mA, the Bragg's angle (2θ) was in the range of 5°–80° using 0.01 step with and 1 s time count). All data were recorded and analyzed using the machine software. To analyze the crystallinity/amorphous nature, the characteristic peaks of drug produced in the PXRD pattern of physical mixture was compared to the PXRD of pure drug.XRD spectra of pure drug and physical mixture was recorted to determine the physical state of drug . [8]

UV spectroscopy of Gabapentin:

Colorimetry method (Ninhydrin)

An accurately weighed 100 mg drug of gabapentin pure drug was dissolved and transferred in a 100 ml volumetric flask containing distilled water and sonicated well. Then the volume was adjusted up to the mark with distilled water to obtain stock (primary) solution of 1000 µg/ml. From the above stock solution, a diluted standard solution with a concentration of 100 µg/ml was prepared.

Different aliquots of drug solution were transferred into test tubes. To each test tube 2 mL of ninhydrin reagent in methanol was added and 10 mL of de-ionized water was added, then test tubes were heated on a water-bath at 70 ± 5 ˚C for 30 min. These solutions were transferred to volumetric flasks after cooling and the volume was made up to the mark with de-ionized water to provide a final concentration range of 5 to 30 mg mL/1. The absorbance of the solution was measured against a reagent blank at 570 nm using UV visible spectrometer. The calibration graph was prepared by plotting absorbance vs concentration of gabapentin. [18]

EVALUATION OF GABPENTIN MATRIX TABLETS:

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using a Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked from each batch and the hardness of the tablets was determined. [19]

Friability test

The friability of tablets was determined using Roche Friabilator. It is expressed in percentages (%). Twenty tablets were initially weighed (w0 initial) and transferred into the Friabilator. The Friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (w). Percentage friability of tablets less than 1% is considered acceptable. [20]
The % friability was then calculated following.
% Friability = $100 (W_1\text{-}W_2/W_1)$

Weight variation test

Twenty tablets were selected at random and the average weight was determined. Not more than two of the individual weights deviate from the average weight by more than the percentage deviation shown in the table and none deviates by more than twice the percentage. USP official limits of percentage deviation of the tablet are presented in the Table. [21]

Drug content:

Aqueous solution of gabapentin was prepared in water and the absorbance was measured at 569 nm using a UV-VIS spectrophotometer. A linear equation was generated for the medium by fitting a weighted linear regression model to the data obtained in triplicate. [13]

SWELLING STUDIES:

The swelling behavior of the dosage unit can be measured either by studying its dimensional changes, weight gain, or water uptake. The water uptake study of the dosage form was

conducted by using USP dissolution apparatus-II in 900 ml of distilled water which was maintained at 37 + 0.5˚C, rotated at 50 rpm. At selected regular intervals the tablet was withdrawn and weighed.%Swelling of the tablet was expressed as percentage water uptake (%WU)

%WU = (Wt - Wo/ Wo) * 100

Where Wt is the weight of the swollen tablet and Wo is the initial weight of the tablet. [22]

IN- VITRO DRUG RELEASE STUDY:

In-vitro dissolution studies of gabapentin tablet was carried out in 0.1 N HCL (PH 1.2, 900 ml, $37^{o}\pm 0.5^{0}$ C), using the USP II paddle apparatus at 100 rpm. Sample (10 ml) were withdrawn at predetermined time intervals, filtered through a 0.45 µm membrane filter, and analysed spectrophotometrically after suitable dilution at 569 nm. An equivalent amount of fresh dissolution medium was added to maintain the volume of the dissolution medium. The absorbance values were converted into the percentage of the drug dissolved using an appropriate equation. Each data point represents the average value of three observations. A dissolution study of selected batches was also conducted in phosphate buffer (pH 7.2). [23]

Kinetic studies:

In vitro drug release data were fitted to kinetic models such as zero-order[24], first-order [25], Higuchi equation [26], Korsemeyer–Peppas equation [27], and Hixson–Crowell equation [28]. The regression analysis wasperformed.

Q_t versus t (zero order)

log Q_t versus t (first order)

Q_t versus square root of t (Higuchi)

log $\%Q_t$ versus log %t (Korsmeymer-Peppas)

Q_t versus cube root of t (Hixson–Crowell)

where Q_t is the amount of gabapentin released at time t.

STABILITY STUDIES:

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light. And to establish a retest for the drug substance or a shelf life for the drug product and recommended storage conditions. The storage conditions used for stability studies were Accelerated conditions (40°C ± 2°C/75% RH). A stability study was carried out for the optimized formulation. Tablets of optimized formulation were striped packed and kept in a humidity chamber at above mention temperature. [29]

Results and discussion:

Preformulation study:

Table 3:Preformulation parameteres

Formulation code	Bulk density (g/ml)	Tap density (g/ml)	Carr's index (%)	Angle of repose (Ɵ)	Hausner's ratio
Gabapentin	0.55±0.02	0.714±0.01	22.2±0.02	48.92±0.46	1.29±0.01
Benecel K4M PH DC	0.4±0.04	0.43±0.02	6.97±0.03	32.63±0.42	1.14±0.03
Benecel K15M PH DC	0.46±0.02	0.48±0.01	4.16±0.02	33.73±0.53	1.12±0.02
Benecel K100M PH DC	0.44±0.03	0.47±0.03	6.38±0.0.3	31.1±0.31	1.13±0.04
Benecel K4: Gabapentin	0.45±0.03	0.50±0.03	11.11±0.03	35.28±0.26	1.19±0.01
Benecel K15: Gabapentin	0.46±0.02	0.49±0.01	18.36±0.01	34.66±0.32	1.21±0.01
Benecel K100: Gabapentin	0.44±0.03	0.52±0.03	15.38±0.03	32.01±0.42	1.19±0.01

The results indicate that the gabapentin has poor flow properties and the benecel grade has good flow properties. When gabapentin is mixed with benecel grades, gabapentin flow property was increased.

Drug-polymer compatibility study

FTIR:

The FTIR spectra obtained for gabapentin and physical mixtures of gabapentin are illustrated in the below figrue. The results showed that the characteristic peaks due to pure gabapentin (N-Hbending, N-H and O-H stretching), Physical mixutre (N-Hbending, N-H and O-H stretching) have appeared without any change in their position.The FTIR spectral analysis showed no evidence of chemical interactions between gabapentin and different grades of Benecel DC.

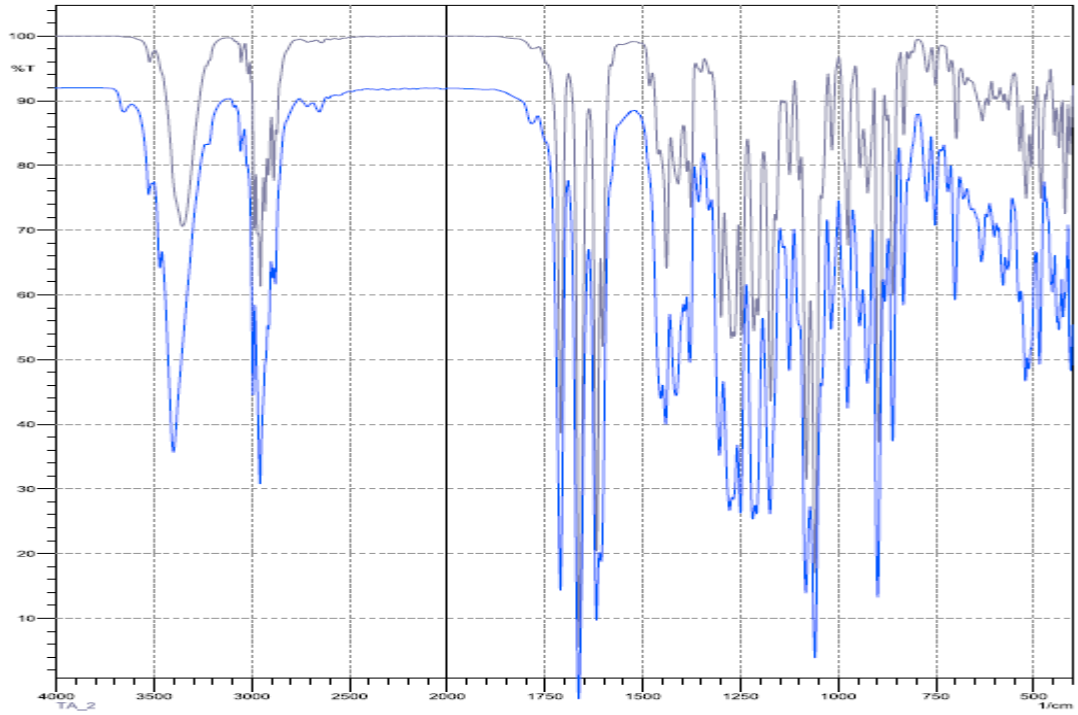

Figure 1:FTIR of drug and physical mixture

DSC method

The DSC thermograms of the physical mixture of gabapentin with Benecel K4M PH DC, Benecel K15M PH DC, and Benecel K100M PH DC, respectively, showed endothermic peaks. Each selected polymer and its respective 1:1 w/w combination are shown in **Fig 2 and 3** together with the thermal profile of pure gabapentin, reported for reference purposes. The sharp melting peak of pure gabapentin at 183 °C and the DSC curves of a 1:1 w/w mixture with all the examined polymeric materials were the simple superimpositions of those of the pure compounds, indicating compatibility of the drug with all the examined polymers.

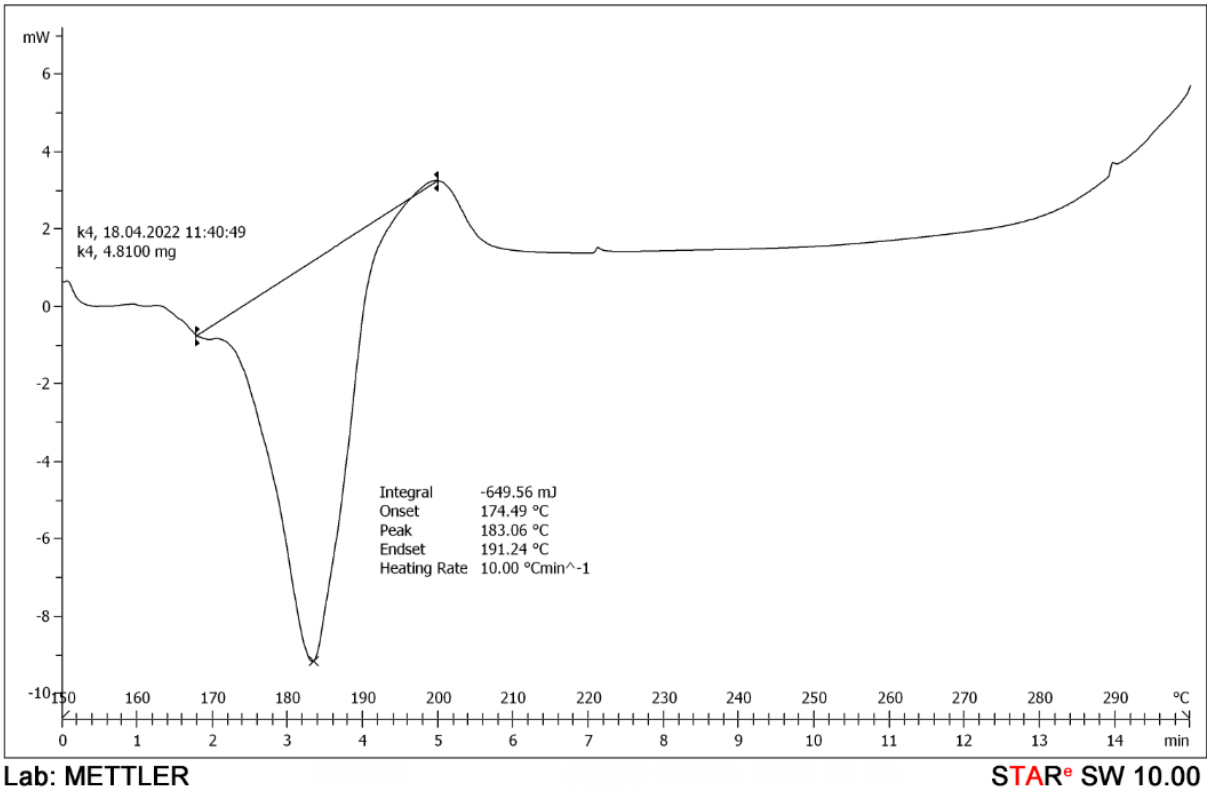

Figure 2:DSC of Drug

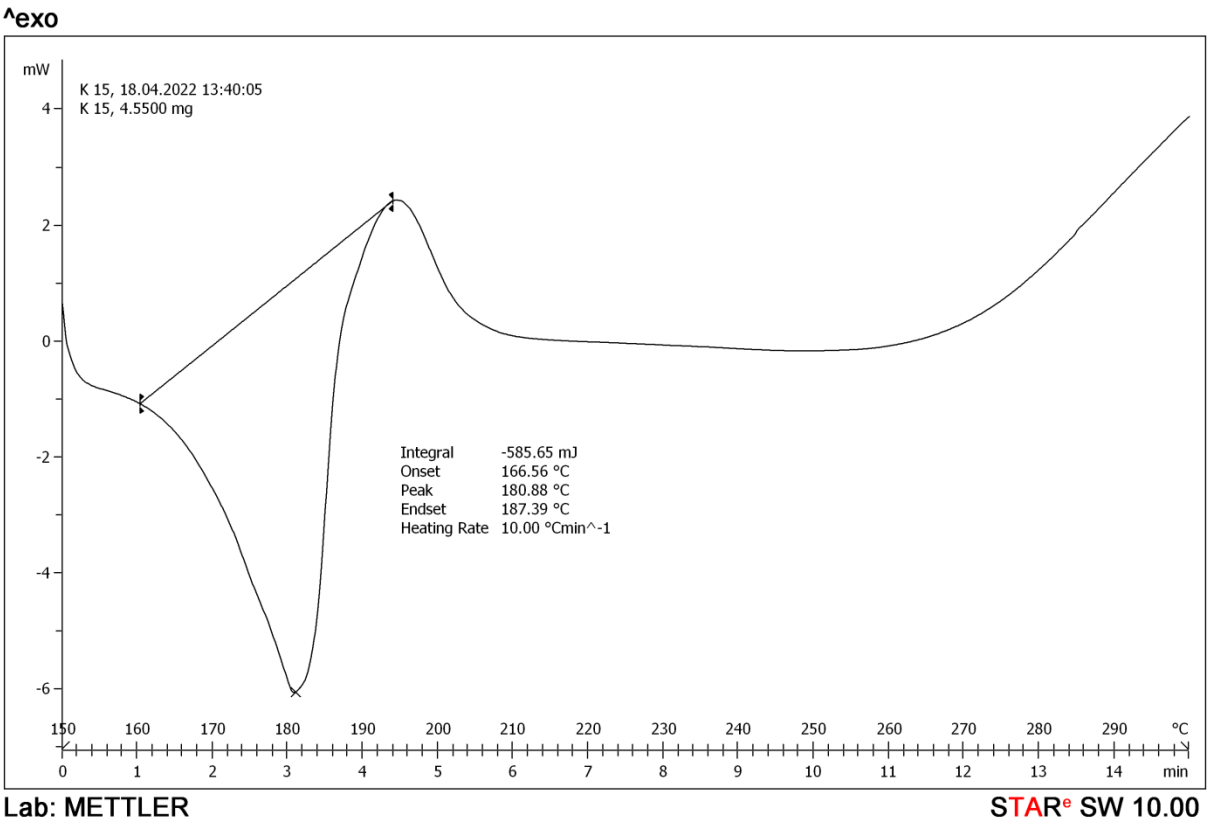

Figure 3:DSC of physical mixture

XRD:

XRD patterns of pure Gabapentin, and the physical mixture of Gabapentin with all excipients was obtained (Fig.4). The major characteristics peaks of Gabapentin can be observed at $2\theta = 15.7$, 19.2, 22.9 and 31. These peaks could be also seen in the physical mixture of the ingredients. XRD patterns of pure Gabapentin revealed that it was in crystalline state before being involved in the developed formula. On the other hand, XRD diffraction patterns of the developed formula showed a broad peak which represents a typical profile of an amorphous material. These patterns assure that Gabapentin physical state was changed from crystalline to amorphous after being involved in the developed formula.

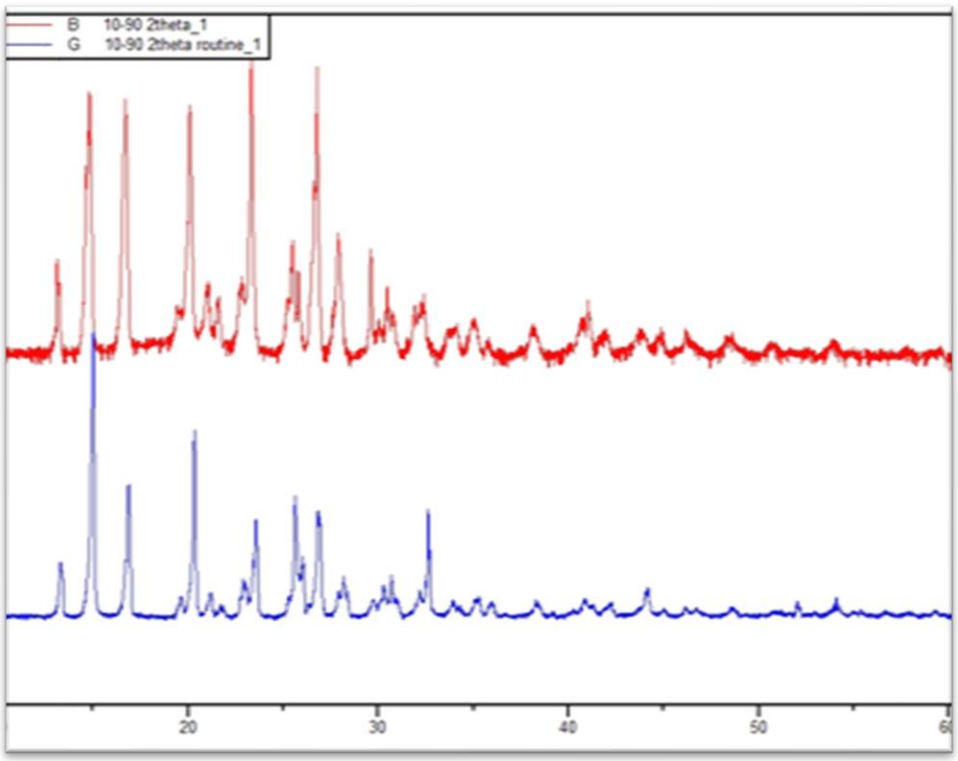

Figure 4:XRD comparision graph of Gabapenin and physical mixture

UV Spectroscopy:

At a wavelength of 569 nm, standard curves of gabapentin were studied in the range of 5-30 µg/ml. Gabapentin chosen range was discovered to be linear. At 569 nm, the regression coefficients were found to be 0.9954.

Post-compression parameters:

The formulated sustained-release matrix tablets were then evaluated for various physical characteristics like thickness, weight variation, hardness, and friability.

Post-compression parameter of formulated tablet

Table 4:Post compression parameters

Formulation code	Average weight (mg)	Thickness (mm)	Hardness (kp/N)	Friability (%w/w)
BK4	600 ±0.29	5. ±0.04	16 ±0.1	0.50 ±0.007
BK15	598 ±0.67	5 ±0.01	16 ±0.5	0.66±0.006
BK100	599 ±0.71	5 ±0.12	16.7 ±0.3	0.50±0.0011
HK100	602 ±0.52	5 ±0.07	16.3 ±0.2	0.66±0.05

Table 4 summarizes the results obtained from the tests conducted on all batches. All batches met the requirement for weight variation test according to USP 32. The disintegration time for the tablets correlated well with their hardness The hardness of the prepared tablets ranged from 16±0.1 to 16.7±0.5, friability values ranged from 0.50 to 0.66, the thickness of tablets was uniform, and values ranged from 5 ± 0.01 to 5. ± 0.12.

Drug content:

The drug content of the prepared tablets were found in range 98.55% to 99.75%.

Percentage swelling index of formulated tablets

Table 5:Swelling Index

Batch code	SWELLING INDEX (%)(mins)							
	15	30	45	60	120	240	360	480
BK4	11.09	16.09	16.09	17.65	20	20.62	20.62	20.62
BK15	10.96	15.28	15.28	16.77	21.42	22.09	23.75	25.74
BK100	16.36	18.18	19.33	19.33	24.62	27.6	29.75	33.88
HK100	7.16	10.61	11.14	11.4	15.91	21.75	23.07	25.72

The swelling behavior of all formulated tablets was calculated and results were ranging from 7.16% to 33.88%.The results are clearly indicating that swelling capacity increases by increasing polymer Viscosity.

In-vitro drug release study:

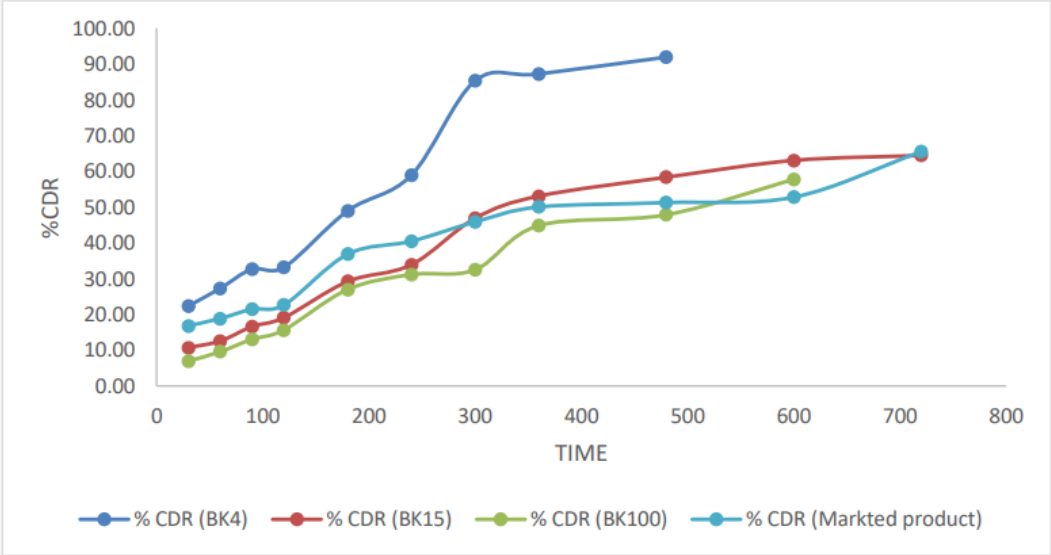

Figure 5: In-vitro drug release study of Gabapentin

The methods used in the dissolution study and the comparison parameters can be used to compare and identify the differences between formulations, in order to establish acceptance criteria and preview how alterations in manufacturing would affect bioavailability. Formulation containing benecel K15 and benecel K100 had given drug release 63.04 % and 57.76 in 10 hrs, responsivity and it matches with marketed product drug release profile.

Kinetic models:

Table 6:Kinetic Models

Sr No.	Formulations	Mathematical models for drug release kinetics				
		Zero-order model	First order model	Hixson and Crowell model	Higuchi model	Korsemeyer-peppas model
		r2	r2	r2	r2	r2
1	BK4	0.9167	0.961	0.9516	0.9728	0.621
2	BK15	0.9546	0.9656	0.9628	0.9419	0.6895
3	BK100	0.9816	0.9831	0.9832	0.921	0.7726
4	HK100	0.9014	0.9317	0.9232	0.9524	0.5968

The kinetic parameters for the *in vitro* release of gabapentin matrix tablets were analyzed in order to find the drug release. Table shows the correlation of excipients to various kinetic models. Thehighest value of r(0.9832) and was found for Bencel K100 with the Hixon and Crowell model.

Stability studies:

Table 7: Stability Sudies

BATCH COAD	DRUG CONTENT		
	INITIAL	SUN LIGHT	75% HUMIDITY
BK4	93.66%	91.60%	96.51%
BK15	101.42%	105.29%	103.48%
BK100	99.35%	97.28%	98.32%
HK100	95.99%	97.70%	98.06%
Marketed formulation	110.78%	-	-

The stability studies for formulation were carried out based on accelerated stability conditions and the study of various parameters was carried out at 4 hr the results found satisfactorily reveals that the formulation was stable under accelerated conditions and there were no changes observed in drug content.

CONCLUSION

The most important characteristic to the direct compression grades of HPMC is the improved flow of the powder. Due to the poor flow of the standard CR grades of HPMC formulations typically require a granulation step. The results indicated that the Benecel DC grades had a significantly better flow than the standard grades. The Preformulation and post-formulation results suggested that the benecel grades are suitable as DC material. The results of the FTIR & DSC study showed that there was no interaction between Gabapentin & benecel grades . The in vitro dissolution study, swelling, and drug content showed good results. According to the industry perspective, the benecel DC grade should provide better performance in direct compression applications than a standard grade of HPMC, as well as reduce process complexity, low cost, and manufacturing cycle time.

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