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Formulation and Selection of Controlled Release Layer for Designing the Paracetamol Sustained Release Tablets Based on In Vitro Profile

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ABSTRACT

This study aimed to design a controlled-release (CR) layer for 700 mg paracetamol using banana starch (BS) and compare it with polyvinyl alcohol (PVA) and hydroxypropyl methylcellulose (HPMC). Tablets were prepared by direct compression and wet granulation methods. A total of 24 CR layers were developed using three polymers at 10%, 15%, 20% and 25% w/w concentrations. Pre-compression parameters (bulk density, tapped density, Carr's index, Hausner's ration and angle of repose) and post-compression parameters (weight variation, hardness, friability and assay) confirmed good mechanical properties. Selected CR layers demonstrated robust manufacturing characteristics and optimal release profiles, suitable for controlled drug delivery. The selected best CR layers were CR2(nearly 90%), CR7 (nearly 98%), CR12 (nearly 97%), CR14(nearly 6%) and CR23 (nearly 97%). CR layers by direct compression, especially with BS, showed superior controlled release CR2 (90%, direct compression) and CR14 (96%, wet granulation) exhibited optimal release, with CR2 being the most effective.

Keywords: *Sustained Release Tablets (SR), Controlled Release (CR) Layer, Banana Starch (BS), Polyvinyl Alcohol (PVA), Hyoxypropyl Methyl Cellulose (HPMC)*

1. INTRODUCTION

Controlled release tablets are intended to deliver drug for longer/extended duration of period to get the therapeutic effect for longer duration of period. Drugs with longer half-life are not fit to design as controlled release tablets , hence they are designed as sustained release tablets. Sustained release tablets consists an immediate layer (IR) to raise drug to the therapeutic level, and a controlled release layer (CR) to extend the therapeutic concentration for longer duration of period. Though IR is essential for raising the drug concentration to the therapeutic level, the CR layer is vital to extend the therapeutic levels for longer duration of period. The duration of extension of time is depending upon type of polymer used as release-retarding agent, concentration of polymer used, and method of preparation of tablet [1]. Current research work was aimed to design and selection a controlled release layer for paracetamol SR tablets, that are intended for fever manage. In this connection BS was tried as release-retarding agent for design of CR layer. BS had ability to form viscous gel upon contact with moisture, because BS consists of amylose & amylopectin. Where amylose forms the dense swollen gel layer upon contact with moisture, amylopectin imparts viscosity and swelling behaviour to BS upon absorption of moisture., and these two ingredients makes BS to form a dense, viscous swollen layer around and slowdowns drug release from tablet by diffusion [2]. BS was used as release-retarding agent at four various concentrations (10, 15, 20, and 25% w/w), the prepared tablets with BS were compared with two synthetic polymers at the same concentrations- PVA & HPMC. All formulations were evaluated and best CR layers were selected based on *in vitro* parameters, especially based on *in vitro* dissolution.

Paracetamol is used in fever management as antipyretic, and it is belongs to non-steroidal anti-inflammatory drug's category. In ailments such as COVID-19, fever is unable to control with conventional dosage forms and require more dose of paracetamol (650 mg) with more frequency of administration. 2.6 mg of paracetamol per day required for management of fever, the dose may crosses maximum safety concentration due its conventional release and may be not safe clinically [3]. Hence, BS was designed to formulate paracetamol SR tablets. Paracetamol tablets were supposed to design with paracetamol 300 mg IR layer and 700 mg CR layer, where IR layer disintegrates and raises paracetamol concentration to the therapeutic level and CR layer maintains paracetamol at therapeutic level for extended duration of period, by releasing drug at slower rate. In this regard, the BS, natural polymer was tried to formulate paracetamol CR layer.

2. MATERIALS AND METHODS

2.1 Materials

Paracetamol, banana starch, polyvinyl alcohol, micro crystalline cellulose, lactose, magnesium stearate and talc. All chemicals obtained as a gift sample from SK. Healthcare Privare Limited, Bolaram, Hyderabad.

2.2 Methods

UV analytical method

A calibration curve for paracetamol was constructed in pH 6.8 phosphate buffer using a double beam UV-Spectrophotometer (Lab India). Paracetamol was incorporated to pH 6.8 phosphate buffer to prepare 1000 µg/mL solution, which was then diluted to obtain concentrations ranging from 2-16 µg/mL. The λ_{max} of paracetamol was detected using a central concentration, and absorbance was measured for all solutions [4]. The calibration curve was plotted, and system suitability was confirmed by calculating R^2 value and results were showed in Table 3 & Figure 1.

Formulation of paracetamol 700 mg CR tablets

CR tablets were prepared using direct compression and wet granulation methods to identify the optimal formulation with effective retardation of drug release from the controlled release layer.

Direct compression method

Table 1: Formulation table for paracetamol 700 mg CR layers prepared by direct compression method

Ingredient	CR1	CR2	CR3	CR4	CR5	CR6	CR7	CR8	CR9	CR10	CR11	CR12
Paracetamol	700	700	700	700	700	700	700	700	700	700	700	700
BS	100	150	200	250	-	-	-	-	-	-	-	-
PVA	-	-	-	-	100	150	200	250	-	-	-	-
HPMC	-	-	-	-	-	-	-	-	100	150	200	250
MCC	180	130	80	30	180	130	80	30	180	130	80	30
Mg. Stearate	10	10	10	10	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10	10	10	10	10
Tablet weight	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000

Paracetamol CR tablets were designed for direct compression method as shown in Table 1 as follows- paracetamol was used at 700mg as a drug, BS, PVA and HPMC were used as release-retarding agents (Polymers) at 10, 15. 20. 25 % weight per tablet. Where, with the use of BS-CR1 to CR4 tablet formulations, with the use of PVA- CR5 to CR8 tablet formulations, and with the use of HPMC-CR9 to CR12 tablet formulations were designed. Micro crystalline cellulose was used as diluent and its concentration depends on remaining ingredient's concentration used, talc as glidant at 1% weight per tablet, and magnesium stearate as lubricant at 1% per tablet weight,

The tablets are prepared by direct compression method was as followed- drug, diluent and polymer are separately sifted via a sieve (#60) , loaded the poly bag and mixed for two minutes. Then, lubricant and glidant were sifted via sieve (#40), loaded above poly bag, and mixed for two minutes. One tablet weight (1000 mg) powder was weighed individually and compressed as tablet by Cadmach 16-station compression machine with the use of 16 mm x 9 mm oblong punches [5].

Wet granulation method

Table 2: Formulation table for paracetamol 700 mg CR layers prepared by wet granulation

Ingredient	CR13	CR14	CR15	CR16	CR17	CR18	CR19	CR20	CR21	CR22	CR23	CR24
Intra-granular												
Paracetamol	700	700	700	700	700	700	700	700	700	700	700	700
BS	100	150	200	250	-	-	-	-	-	-	-	-

PVA	-	-	-	-	100	150	200	250	-	-	-	-
HPMC	-	-	-	-	-	-	-	-	100	150	200	250
Lactose	30	30	30	30	30	30	30	30	30	30	30	30
Extra-granular												
Lactose	150	100	50	-	150	100	50	-	150	100	50	-
Mg. Stearate	10	10	10	10	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10	10	10	10	10
Tablet weight	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000

The procedure for preparation of paracetamol CR tablets were designed for direct compression method (Components as per Table 2) as follows- paracetamol was used at 700mg as a drug, BS, PVA and HPMC were used as release-retarding agents (Polymers) at 10, 15. 20. 25 % weight per tablet. Where, with the use of BS-CR13 to CR16 tablet formulations, with the use of PVA- CR17 to CR20 tablet formulations, and with the use of HPMC-CR21 to CR24 tablet formulations were designed. Lactose was used as diluent and its concentration depends on remaining ingredient's concentration used, talc as glidant at 1% weight per tablet, and magnesium stearate as lubricant at 1% per tablet weight. Where. paracetamol, polymer and some part of lactose were used as intra-granular and remaining ingredients as extra-granular agents.

Procedure for preparation for paracetamol 700 mg CR tablets by wet granulation method was as followed- drug, polymer, and some part of diluent are separately sifted via sieve (#60), loaded to the mortar, and prepared a dough mass with the sprinkling of water. Dough mass is sifted via sieve (# 20), and granules are dried in a hot air oven for 60 minutes by maintaining 60 ^{0}C, and are loaded to poly bag. Then, the remaining ingredients- remain part of diluent, lubricant and glidant are sifted via sieve (#40), loaded to above poly bag, and mixed for two minutes. One tablet weight (1000 mg) powder was weighed individually and compressed as tablet by Cadmach 16-station compression machine with the use of 16 mm x 9 mm oblong punches [6].

2.3 Evaluation of paracetamol 700 mg CR Tablets

Pre-compression parameters

Bulk density

10 ml of measuring cylinder is weighed, and weight was noted as W_1. It is filled with paracetamol CR tablet powder mix and weight was noted as W_2, as well the volume was noted as V. The bulk density for paracetamol CR tablet powder mix was calculated by following equation[13,14],

Bulk Density = $[(W_2-W_1)/V]$

Tapped Density

10 ml of measuring cylinder is weighed, and weight was noted as W_1,. It is filled with paracetamol CR tablet powder mix and weight was noted as W_2. The measuring cylinder's mouth was tied with a butter paper and placed in a Kshitij Bulk density apparatus and allowed for 100 tapping [7]. Tapped density of paracetamol CR tablet powder mix was calculated by,

Tapped Density = $[(W_2-W_1)/V]$

Carr's Index

Carr's index is calculated for paracetamol CR tablet powder mixtures by following equation [8].

Carr's Index = {[(Tapped Density-Bulk Density)/Tapped Density] x 100}

Acceptance criteria for paracetamol CR tablet powder mix was <40%.

Hausner's Ratio

Hausner's ratio is calculated for paracetamol CR tablet powder mixtures by following equation [9].

Hausner's Ratio = (Tapped Density/Bulk Density)

Acceptance criteria for paracetamol CR tablet powder mix was <1.35.

Angle of Repose

A graph paper was placed on a working bench underneath a funnel tip, a two centimetre apart. paracetamol CR tablet powder mix from each batch was separately passed through glass funnel until flow stops. Then, the diameter of pile is calculated and considered as "D" and distance between tip of funnel to graph paper was considered as "h", and using these two parameters the Angle of repose is assessed by following formula[10],

$$Angle\ of\ Repose(\theta) = Tan^{-1}\ (2h/D)$$

Acceptance criteria for paracetamol CR tablet powder mix was <40°

Post-compression evaluation

Weight variation

Twenty tablets were randomly selected, and their individual weights were measured. The average weight was then calculated. Using the individual weight of each tablet and the average weight, the weight variation is calculated by [11]

$$Weight\ Variation\ (\%) = \{[(Individual\ Mass - Average\ Mass)/Average\ Mass]x100\}$$

Limits of acceptance criteria is ±5% for weight variation of these paracetamol CR tablets, because of their individual tablet weight is more than 250 mg.

Hardness Test

A random sample of five dosage units are selected from each production lot of CR tablets and hardness was measured by Monsanto hardness tester, and the acceptance criteria for hardness is ±5% for each CR tablet batch [12].

Friability

A random sample of ten dosage units selected from each production lot of CR tablets, weight was measured and considered as initial weight, W_1. Ten tablets were subjected to friability testing in a friabilator (Kshitij), where they were rotated by 25 rpm for a duration of four minutes, and were with drawn from friabilator. Each tablets was cleaned with a soft cloth and weight of all ten tablets were measures, and was considered as final weight, W_2. % friability was calculated by considering W1 & W2 values by using following equation,

$$Friability\ (\%) = \{[(W1 - W2)/W1] \times 100\}$$

Acceptance criteria for all CR tablets was % friability should be <1% for all paracetamol CR tablets [13].

In vitro dissolution Test

Six tablets are randomly selected from each batch and immersed in 900 mL pH 6.8 phosphate buffer, maintained at a temperature of 37±0.5°C. The solution was intervals stirred at 50 rpm using a paddle (USP Apparatus II). At predetermined time intervals as showed in Table 6 & 7, 5 mL samples were withdrawn and replaced with an equal volume of pH 6.8 phosphate buffer. Samples were diluted preporely and evaluated using Lab India Double Beam UV-Spectro Photo meter at 245 nm to know the Cumulative % Drug Release using following formula [29,30], with the use of absorbance of test(A_T), absorbance of standard (A_S), dilution of test (D_T) and dilution of standard (D_S).

$$Cumulative\ \%\ Drug\ Released = [(A_T/A_S) \times (D_S/D_T) \times 100]$$

Assay

20 tablets were picked from each batch of CR tablets and grounded finely in a mortar with the help of pestle. One tablet weight of powder was picked from mortar, dissolved in pH 6.8 phosphate buffer, and samples are preporely diluted, and evaluated using Lab India Double Beam UV-Spectro Photo meter at 245 nm and evaluated % assay using follow equitation [14,15] with the use of absorbance of test(A_T), absorbance of standard (A_S), dilution of test (D_T) and dilution of standard (D_S).

$$\%\ Assay = [(A_T/A_S) \times (D_S/D_T)]$$

The acceptance criteria for % assay is 90% to 110%.

3. RESULTS & DISCUSSION

3.1 UV analytical method

Table 3: Standard calibration graph of paracetamol in pH 6.8 phosphate buffer

Concentration (µg/ml)	Absorbance
2	0.113 ± 0.009
4	0.226 ± 0.012
6	0.339 ± 0.024
8	0.452 ± 0.035
10	0.565 ± 0.042
12	0.678 ± 0.041
14	0.791 ± 0.057
16	0.904 ± 0.065

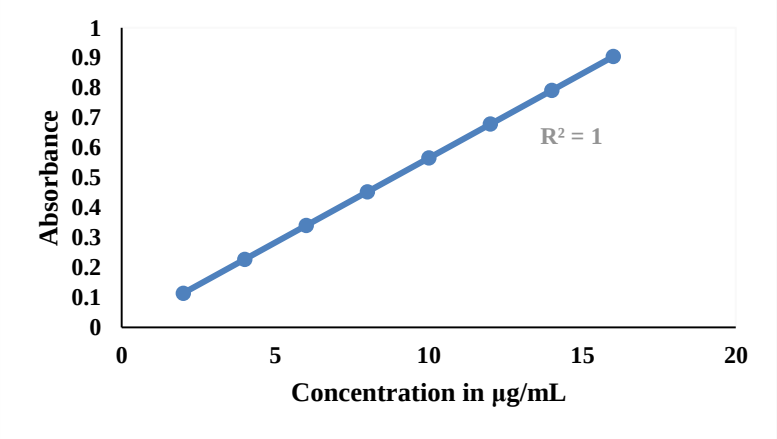

Figure 1: Standard calibration graph of paracetamol in pH 6.8 phosphate buffer

The λ_{max} of paracetamol in pH 6.8 phosphate buffer was observed to be 245 nm, which matched the standard reference value. This confirmed the identity of the analyzed substance as paracetamol using UV-Spectrophotometry.

From the Table 3 & Figure 1, it was observed that the R^2 value of standard curve of paracetamol in pH 6.8 phosphate buffer was observed to be 0.999 at concentration range between 2 to 16 µg/mL, measured at 245 nm. Hence, it was confirmed that these concentration ranges producing linearity in estimation and obeying Beer-Lambert's law, and UV-Spectro photo meter was accurate and could be able to analyse paracetamol in various formulations.

3.2 Pre-compression evaluation

Table 4: Pre-compression evaluation for paracetamol 700 mg CR tablets (Layers)

Formulation Code	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (°)
CR1	0.46 ± 002	0.59 ± 0.03	23.08 ± 1.24	1.30 ± 0.09	34 ± 2.22
CR2	0.47 ± 0.03	0.62 ± 0.04	23.81 ± 2.02	1.31 ± 0.08	29 ± 2.34

CR3	0.42 ± 0.02	0.55 ± 0.03	24.56 ± 1.53	1.32 ± 0.08	32 ± 2.43
CR4	0.48 ± 0.01	0.63 ± 0.03	23.44 ± 1.70	1.30 ± 0.01	30 ± 2.44
CR5	0.49 ± 0.02	0.64 ± 0.04	22.58 ± 2.03	1.29 ± 0.09	31 ± 2.43
CR6	0.45 ± 0.01	0.59 ± 0.03	23.73 ± 1.99	1.31 ± 0.12	35 ± 2.82
CR7	0.50 ± 0.02	0.65 ± 0.05	22.81 ± 2.12	1.29 ± 0.09	28 ± 2.11
CR8	0.44 ± 0.02	0.58 ± 0.04	24.19 ± 2.21	1.32 ± 0.11	33 ± 2.94
CR9	0.47 ± 0.03	0.61 ± 0.03	23.33 ± 1.83	1.30 ± 0.09	29 ± 2.35
CR10	0.48 ± 0.02	0.62 ± 0.05	22.95 ± 1.34	1.31 ± 0.08	30 ± 2.43
CR11	0.50 ± 0.03	0.65 ± 0.05	23.08 ± 2.16	1.30 ± 0.11	31 ± 2.86
CR12	0.45 ± 0.02	0.59 ± 0.03	24.14 ± 2.10	1.32 ± 0.10	32 ± 2.94
CR13	0.46 ± 0.02	0.60 ± 0.04	23.44 ± 1.26	1.31 ± 0.09	30 ± 2.44
CR14	0.43 ± 0.03	0.57 ± 0.03	23.73 ± 1.11	1.31 ± 0.05	34 ± 2.99
CR15	0.48 ± 0.03	0.63 ± 0.04	23.81 ± 1.08	1.30 ± 0.09	29 ± 2.05
CR16	0.49 ± 0.02	0.64 ± 0.04	22.41 ± 2.04	1.29 ± 0.09	30 ± 2.46
CR17	0.45 ± 0.03	0.58 ± 0.02	23.21 ± 0.94	1.30 ± 0.11	32 ± 3.01
CR18	0.44 ± 0.02	0.58 ± 0.03	23.08 ± 1.82	1.30 ± 0.09	31 ± 2.92
CR19	0.46 ± 0.01	0.60 ± 0.04	22.81 ± 0.86	1.30 ± 0.06	34 ± 3.05
CR20	0.47 ± 0.03	0.61 ± 0.05	23.33 ± 2.06	1.31 ± 0.09	35 ± 3.16
CR21	0.42 ± 0.02	0.55 ± 0.04	24.56 ± 2.34	1.32 ± 0.08	33 ± 3.00
CR22	0.50 ± 0.03	0.64 ± 0.05	23.44 ± 2.00	1.30 ± 0.11	28 ± 2.24
CR23	0.49 ± 0.01	0.65 ± 0.03	22.95 ± 2.02	1.31 ± 0.06	32 ± 2.48
CR24	0.48 ± 0.03	0.63 ± 0.03	24.19 ± 1.34	1.31 ± 0.09	30 ± 1.98

From the Table 4, it was observed that the pre-compression parameters for for all the paracetamol CR tablet mixtures was found to be as follows- bulk density values are in between 0.42 to 0.50 g/cm^3, tapped density values are in between 0.55 to 0.65 gm/cm^3. Carr's index values are ranged from 22.41 to 24.56% and Hausner's ratio findings are in between 1.29 to 1.32.

Inferences for above observations are as follows- low bulk density of all tablet powder mixtures from CR1 to CR24 indicates good flow properties and great compactness. A high tapped density compared to bulk density indicates good compressibility for all mixtures, a good characteristic for tableting. With respect to values of all tablet powder mixes have values for Carr's index & Hausner's ratio values are within acceptable limits, hence, all the powders could able to compress as tablets because of their goo flow properties. Finally, based on all pre-compression characteristics, it was found to be all tablet powder mixture from CR1 to CR24 were able and capable to compress as tablet formulations.

3.3 Post-compression evaluation

Table 5: Post-compression evaluation findings for paracetamol 700 mg CR tablets (Layers)

Formulation Code	Weight variation (%)	**Hardness** (kg/cm^2)	**Friability (%)**	**Assay** (%)
CR1	3.16 ± 0.18	6.5 ± 0.35	0.34 ± 0.02	98.54 ± 8.24

CR2	4.17 ± 0.34	6.2 ± 0.42	0.29 ± 0.01	99.05 ± 7.46
CR3	2.60 ± 0.09	6.4 ± 0.46	0.43 ± 0.03	98.29 ± 2.48
CR4	1.93 ± 0.09	6.3 ± 0.37	0.51 ± 0.03	99.65 ± 8.46
CR5	4.24 ± 0.13	6.8 ± 0.43	0.24 ± 0.01	98.84 ± 6.65
CR6	3.63 ± 0.21	7.0 ± 0.52	0.46 ± 0.02	99.75 ± 9.02
CR7	3.65 ± 0.30	6.6 ± 0.49	0.34 ± 0.02	98.83 ± 2.42
CR8	3.18 ± 0.24	6.7 ± 0.54	0.73 ± 0.05	99.27 ± 8.45
CR9	2.12 ± 0.18	6.9 ± 0.50	0.66 ± 0.05	98.46 ± 8.42
CR10	4.04 ± 0.32	6.0 ± 0.33	0.54 ±0.04	99.08 ± 8.34
CR11	2.82 ± 0.11	6.4 ± 0.51	0.37 ± 0.02	98.74 ± 7.92
CR12	3.81 ± 0.17	6.8 ± 0.38	0.42 ± 0.03	99.55 ± 9.05
CR13	3.57 ± 0.22	6.1 ± 0.40	0.58 ± 0.04	98.76 ± 8.42
CR14	4.12 ± 0.38	6.4 ± 0.42	0.41 ± 0.03	98.46 ± 6.24
CR15	3.11 ± 0.29	6.2 ± 0.38	0.72 ± 0.02	99.48 ± 5.45
CR16	2.46 ± 0.13	6.7 ± 0.44	0.64 ± 0.03	99.37 ± 4.28
CR17	2.72 ± 0.11	7.1 ± 0.58	0.68 ±0.03	99.43 ± 8.45
CR18	4.09 ± 0.28	6.8 ± 0.48	0.18 ± 0.01	98.91 ± 8.47
CR19	2.25 ± 0.15	6.8 ± 0.50	0.27 ± 0.01	99.86 ± 6.83
CR20	3.38 ± 0.30	6.7 ± 0.53	0.32 ± 0.01	99.59 ± 7.52
CR21	3.57 ± 0.24	6.5 ± 0.38	0.43 ± 0.02	98.93 ± 8.75
CR22	4.10 ± 0.28	6.4 ± 0.35	0.44 ± 0.03	99.73 ± 6.76
CR23	2.48 ± 0.16	6.2 ± 0.48	0.46 ± 0.02	98.67 ± 5.91
CR24	4.15 ± 0.25	6.5 ± 0.29	0.62 ± 0.04	99.16 ± 6.98

Post-compression values for all the paracetamol CR tablets for CR1 to CR24 showed in Table 5 and are as follows- the weight variation values are in between 1.93 to 4.24%, hardness values are in between 6.0 to 7.1 kg/cm^2, and friability values are in between 0.10 to 0.73%, and assay values are in between 98.29 to 99.86%.

The observations from post-compression parameters of all tablet formulations from CR1 to CR24 inferences that, all the formulations weight variation was with in the acceptance limits indicates that uniformity in tablet weight. Hardness values indicates that tablets had good mechanical strength and tablets may possess good physical stability to with stand various mechanical agitations that tablet experience while packing, shipping and etc. The friability values indicates tablets may with stand to breakage while handling. And the assay values were assured uniformity of dose foe all formulations from CR1 to CR24.

3.4 In vitro dissolution Data

Direct compression method

Table 6: *In vitro* dissolution profile for CR formulations by Direct compression (CR1 to CR12)

Time (hours)	CR1	CR2	CR3	CR4	CR5	CR6	CR7	CR8	CR9	CR10	CR11	CR12
0	0	0	0	0	0	0	0	0	0	0	0	0
0.5	4.98	5.19	4.03	3.02	7.07	7.09	3.58	4.97	6.19	7.36	4.59	5.09
1	10.02	10.02	7.26	8.03	11.99	10.78	9.31	10.55	15.04	12.66	13.69	10.83

1.5	14.64	12.36	10.08	11.50	17.68	15.69	13.98	11.04	22.69	18.14	16.36	14.79
2	21.56	19.25	15.07	13.84	26.37	22.35	17.33	15.12	29.44	26.46	21.02	19.25
3	29.42	25.99	23.06	19.11	35.77	30.11	27.36	22.05	41.22	36.87	30.16	26.30
4	40.73	34.25	27.96	23.22	47.58	40.39	35.47	28.39	55.17	50.14	39.40	32.60
5	49.23	39.89	36.25	31.53	62.69	50.14	40.12	32.21	69.07	60.36	48.68	39.48
6	61.52	46.28	39.63	38.36	73.54	62.50	49.33	40.13	83.25	72.49	57.98	47.49
7	69.32	49.03	45.69	41.09	83.11	72.34	57.14	46.93	97.13	86.50	68.37	57.43
8	81.89	60.36	53.54	42.36	95.03	80.98	65.46	50.34	-	96.48	75.96	65.79
9	89.64	69.58	59.59	53.25	-	92.89	75.59	58.89	-	-	86.79	73.89
10	100.00	75.42	64.36	62.34	-	100.00	82.38	63.79	-	-	94.46	81.69
11	-	82.81	72.39	66.96	-	-	91.85	69.25	-	-	100.00	88.66
12	-	89.73	76.22	72.46	-	-	98.05	75.66	-	-	-	96.79

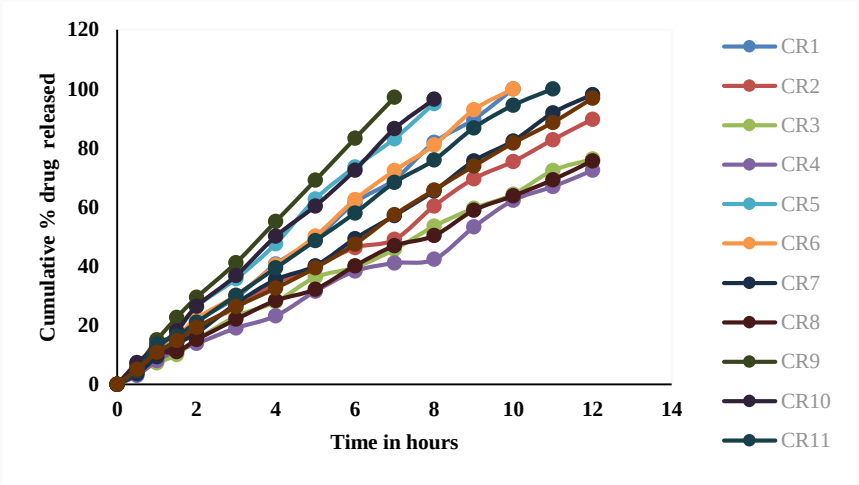

Figure 2: *In vitro* dissolution profile for CR formulations by Direct compression (CR1 to CR12)

A two-way ANOVA was conducted to evaluate the effects of time and formulation on the *in vitro* dissolution profile for tablets prepared by direct compression method (shown at Table 6). The analysis revealed a significant main effect of time ($F(14,158) = 1177.15$, $p < 0.0001$), indicating a substantial increase in drug release over time. Similarly, the formulation factor showed a significant effect ($F(11,158) = 329.64$, $p < 0.0001$), confirming that different formulations exhibited distinct dissolution behaviors. Additionally, the interaction effect between time and formulation was statistically significant ($F(154,158) = 5.26$, $p < 0.0001$), suggesting that the dissolution rate varied depending on the specific formulation used at each time point. The total sum of squares for time, formulation, and their interaction were 117095.46, 25764.35, and 5756.91, respectively, with a residual error of 1092.32. these findings confirm that both formulation composition and time significantly influence drug dissolution, and their interaction plays a crucial role in modulating release kinetics.

From the Table 6 and Figure 2, it was observed that, formulation designed with BS-CR1, CR2, CR3 and CR4 are releasing approximately 100% at 10^{th} hour, approximately 90%, 76% and 72% at 12^{th} hour. The ascending order of formulations based on their *in vitro* dissolution are a follows for formulations designed with BS as release-retarding agent as follows,

CR4 < CR3 < CR2 < CR1

From the Table 6, it was observed that, formulation designed with PVA-CR5, CR6, CR7 and CR8 are releasing approximately 95 at 8^{th} hour, 100% at 10^{th} hour, 98% and 76% at 12^{th} hour, and the ascending order of formulations based on their *in vitro* dissolution are a follows for formulations designed with PVA as release-retarding agent as follows,

CR8 < CR7 < CR6 < CR5

From the Table 6, it was observed that, formulation designed with HPMC-CR9, CR10, CR11 and CR12 are releasing paracetamol approximately 97% 7^{th} hour, approximately 96% at 8^{th} hour, 100% at 11^{th} hour and 97% at 12^{th} hour, and the ascending order of formulations based on their *in vitro* dissolution are a follows for formulations designed with HPMC as release-retarding agent as follows,

CR12 < CR11 < CR10 < CR9

Wet granulation method

Table 7: *In vitro* dissolution profile of CR formulations by wet granulation

Time (hours)	CR13	CR14	CR15	CR16	CR17	CR18	CR19	CR20	Cr21	CR22	CR23	CR24
0	0	0	0	0	0	0	0	0	0	0	0	0
0.5	4.33	3.58	2.44	1.90	5.46	4.31	3.58	2.47	6.98	5.65	4.36	3.79
1	9.56	8.43	7.52	6.23	10.03	9.36	8.13	7.25	11.35	10.33	9.49	8.36
1.5	14.58	12.36	10.79	8.51	15.34	13.94	11.64	9.29	16.49	14.89	12.06	10.47
2	19.14	16.69	14.36	12.25	20.49	17.79	14.42	11.22	21.19	18.85	15.94	12.43
3	27.79	23.55	19.46	15.84	30.04	26.89	22.40	18.96	33.46	28.86	24.44	20.99
4	35.66	30.94	24.20	20.49	40.43	35.49	30.99	23.49	45.51	38.22	32.91	27.17
5	43.49	37.88	29.03	25.97	50.63	44.57	36.49	28.44	57.69	48.64	40.19	33.25
6	51.36	44.79	34.98	30.84	60.93	53.64	42.28	33.13	69.33	58.79	48.94	39.82
7	59.47	51.46	39.79	35.49	70.64	62.98	48.14	38.14	81.11	68.71	56.31	45.46
8	67.78	58.97	44.89	40.13	80.46	71.49	54.85	43.32	93.05	78.05	64.84	51.21
9	75.49	65.48	49.90	45.01	90.79	80.79	60.94	48.34	-	88.94	72.58	57.01
10	83.88	72.33	54.46	50.94	100.00	89.51	66.84	53.49	-	98.08	80.48	63.84
11	91.44	79.11	59.2	55.07	-	98.50	72.31	58.59	-	-	88.94	69.84
12	99.06	86.09	64.04	60.99	-	-	78.41	63.36	-	-	96.5	75.96

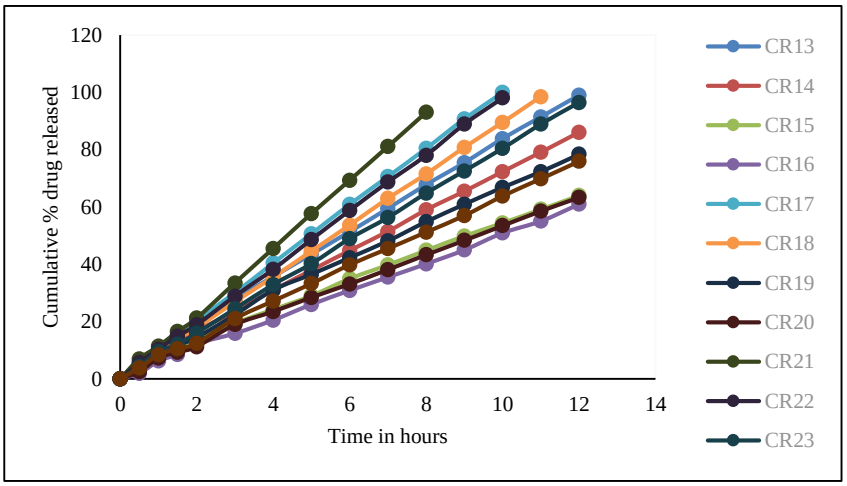

Figure 3: *In vitro* dissolution profile of CR formulations by wet granulation

A two-way ANOVA was performed to assess the impact of time and formulation on the *in vitro* dissolution profile of the formulations prepared by wet granulation method (shown at Table 7). The analysis demonstrated a highly significant effect of time ($F(14, 158) = 1156.23$, $p < 0.0001$), indicating a progressive increase in drug release over the dissolution period. The formulation factor also showed a significant influence on the dissolution profile ($F(11, 158) = 312.79$, $p < 0.0001$), confirming that variations in formulation composition led to distinct drug release patterns. Furthermore, the interaction effect between time and formulation was statistically significant ($F(154,158) = 4.92$, $p < 0.0001$), suggesting that the dissolution rate of each formulation was influenced by the specific formulation characteristics over time. The total sum of squares for time, formulation, and their interaction were 113245.67, 24578.92, and 5543.76 respectively with a residual error of 1085.34. these results confirm that both time and formulation significantly affect drug release, and their interaction plays a key role in determining dissolution kinetics.

As per the findings of Table 7 and Figure 3, the paracetamol 700 mg CR tablets designed with BS-C13, CR14, CR15 and CR16 are releasing approximately 99, 86, 64 and 61% paracetamol at 12th hour, and the ascending order of formulations based on their *in vitro* dissolution are a follows for formulations designed with BS as release-retarding agent as follows,

CR16 < CR15 < CR14 < CR13

As per the findings in Table 7, paracetamol 700 mg CR tablets designed with PVA-C17, CR18, CR19 and CR20 are releasing paracetamol 100% at 10th hour, 98% at 11th hour , 78% at 12th hour, and 68% at 12th hour. The ascending order of formulations based on their *in vitro* dissolution are as follows for formulations designed with PVA as release-retarding agent as follows,

CR20 < CR19 < CR18 < CR17

As per the findings in Table 7, paracetamol 700 mg CR tablets designed with HPMC-CR21, CR22, CR23 and CR24 were releasing paracetamol approximately 93% at 8th hour, 98% at 10th hour , 96% at 12th hour, and 76% 12th hour. The ascending order of formulations based on their *in vitro* dissolution are a follows for formulations designed with HPMC as release-retarding agent as follows,

CR24 < CR23 < CR22 < CR21

The dissolution profile of paracetamol CR tablets revealed that the release of drug was significantly retarded by release-retarding agent i.e. polymer. Notably, the extent of retardation increases with the concentration of polymer. Specifically, among the formulations containing 25% w/w polymer, the order of increasing retardation effect is as follows

CR16 < CR20 < CR4 < CR8 < CR4 < CR12

According to USP specifications drug should release not less than 85% at the end of 12th hour [33]. With respect to USP specifications only CR2 (approximately 90%), CR7 (approximately 98%) and CR12 (97%) are considerable CR layers from direct compression, and CR13 (approximately 99%), CR14 (86%) and CR23 (96%) are considerable CR layers for designing of paracetamol SR tablets. Among these, except CR13 all remaining CR layers were selected as best CR layers for design and formulation of paracetamol SR tablets. CR13 was showing approximately 100% *in vitro* drug release at 12th hour, hence it was considered that it may not be fit for more controlling release of drug from CR layer. And ascending order of the best CR layers with respect to their *in vitro* drug release at the end of 12th hour was as follows,

CR14 (Approximately 86%) < CR2 (Approximately 90%) < CR23 (96.5%) < CR12 (96.79) < CR7 (98%)

It was concluded that CR14 was showing good control of drug release compared to other layers, it is designed with the help of BS, as well next to CR14 CR12 is the best release-retarding agent. It is also prepared with the help of BS, a natural release-retarding agent (polymer). Hence, here we conclude that BS can be considered as a good release-retarding agent (polymer) for designing of CR formulations or CR layers for SR formulations.

***In vitro* drug release kinetic Data**

Table 8: *In vitro* drug release kinetic data for all CR tablets (Layers) from CR1 to CR24

Formulation Code	Zero-order (R^2)	First-order (R^2)	Higuchi (n)	Korsmeyer-Peppas (n)
CR1	0.999 ± 008	0.871 ± 0.07	0.932 ± 008	0.999 ± 0.09
CR2	0.996 ± 0.06	0.868 ± 0.06	0.944 ± 0.07	0.997 ± 0.09
CR3	0.997 ± 0.05	0.856 ± 0.08	0.949 ± 0.08	0.998 ± 0.08
CR4	0.993 ± 0.07	0.849 ± 0.07	0.930 ± 0.08	0.991 ± 0.07
CR5	0.999 ± 0.08	0.895 ± 0.05	0.929 ± 0.07	0.997 ± 0.05
CR6	0.999 ± 0.08	0.903 ± 0.07	0.932 ± 0.08	0.995 ± 0.08
CR7	0.999 ± 0.07	0.837 ± 0.08	0.939 ± 0.06	0.995 ± 0.07
CR8	0.998 ± 0.08	0.884 ± 0.08	0.948 ± 0.06	0.993 ± 0.08
CR9	0.999 ± 0.06	0.862 ± 0.05	0.925 ± 0.08	0.995 ± 0.07
CR10	0.999 ± 0.07	0.898 ± 0.08	0.929 ± 0.09	0.998 ± 0.05
CR11	0.998 ± 0.08	0.842 ± 0.07	0.946 ± 0.09	0.990 ± 0.06
CR12	0.999 ± 0.08	0.877 ± 005	0.938 ± 0.08	0.997 ± 0.09
CR13	0.999 ± 0.05	0.884 ± 0.07	0.943 ± 0.08	0.998 ± 0.05

CR14	0.998 ± 0.07	0.870 ± 0.05	0.947 ± 0.07	0.996 ± 0.08
CR15	0.999 ± 0.08	0.856 ± 0.06	0.937 ± 0.06	0.994 ± 0.08
CR16	0.997 ± 0.06	0.849 ± 0.07	0.926 ± 0.05	0.993 ± 0.07
CR17	0.999 ± 008	0.898 ± 0.07	0.950 ± 0.07	0.995 ± 0.08
CR18	0.998 ± 0.07	0.878 ± 0.07	0.942 ± 0.08	0.994 ± 0.08
CR19	0.999 ± 0.09	0.868 ± 0.06	0.947 ± 0.08	0.997 ± 0.08
CR20	0.997 ± 0.08	0.890 ± 0.05	0.929 ± 0.09	0.997 ± 0.06
CR21	0.999 ± 0.09	0.863 ± 0.06	0.940 ± 0.08	0.994 ± 0.07
CR22	0.997 ± 0.08	0.875 ± 0.08	0.933 ± 0.08	0.996 ± 0.08
CR23	0.999 ± 0.09	0.855 ± 0.07	0.941 ± 0.08	0.997 ± 0.08
CR24	0.999 ± 0.08	0.872 ± 0.07	0.944 ± 0.07	0.995 ± 0.08

Table 8 reveals that the correlation coefficient (R^2) values for zero-order plots ranged from 0.993 to 0.999, while values for first-order plots ranged from 0.837 to 0.903. The 'n' value for Higuchi plots ranged from 0.925 to 0.950, and values for Korsmeyer-Peppas plots ranged from 0.990 to 0.999.

Based on the *in vitro* pharmacokinetic data, it can be inferred that the release from all CR tables follows a zero-order release pattern. The mechanism of drug release from these tablets appears to be governed by diffusion, specifically non-Fickian diffusion, also known as anomalous transport.

4. CONCLUSIONS

UV- Spectro Phto meter, double beam is suitable to analyse paracetamol in various formulations that are used to analyse by it, because paracetamol in pH 6.8 phosphate buffer at concentration range 2 to 16 g/mL was obeying Beer-Lambert's law by showing linearity (R2 value = 0.999), as shown in Figure 1. And the drug used was identified as paracetamol because it was showing 245 nm (Lambda max) in pH 6.8 phosphate buffer, when analyzed with the help of UV- Spectro Phto meter, double beam. Paracetamol CR layers are feasible to compress as tablets because of their good flow properties that were analyzed by pre-compression parameters as shown in Table 4. Paracetamol CR layers are having good mechanical strength to handle them feasibly, this was came to know from various post-compaction parameters as exhibited in Table 5. *In vitro* drug dissolution of paracetamol from all CR layers as shown in Tables 6 & 7, it was concluded that BS was showing better control of paracetamol *in vitro* releae compared to remaining two release-retarding agents (PVA & HPMC). Especially, direct compression method have shown dominant control of paracetamol from CR layer compared to wet granulation method. Further optimization of CR layers with changing concentration to be used, and different method of preparation may bring better results to design very good paracetamol SR tablets. But finally, CR2, CR7, CR12, CR14 and CR23 layers were selected as best layers for designing of paracetamol SR tablets. Among these CR2, & CR14 were designed with the help of BS, and CR2 manufactured by direct compaction technique and CR14 manufactured by wet granulation technique. These two layers are showing best retardation of drug release compared to other release-retarding agents, hence we can conclude that natural substance (BS) were having best rate release retarding capability compared to synthetic substances (PVA & HPMC) out of this research. The optimal CR layers selected exhibited zero-order release kinetics, releasing paracetamol primarily through non-Fickian diffusion, characterized by anomalous transport mechanisms.

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