RESEARCH ARTICLE

Formulation and Selection of Immediate Release Layer for Designing the Paracetamol Sustained Release Tablets Based on *In vitro* Profile

Kundharaju R, Kumar CSP*

Faculty of Pharmacy, Bir Tikendrajit University, Iamsang, Manipur, India

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ABSTRACT

This study focused on designing paracetamol immediate release (IR) layers using three disintegrants- Banana starch (BS), Sodium starch glycolate (SSG), and Croscarmellose sodium (CCS)- at concentrations of 2%, 4%, 6%, and 8% (w/w).A total of 24 formulations are prepared: 12 via direct compression (IL1-IL12) and 12 via wet granulation (IL13-IL24). Pre-compression properties (bulk density: 0.45-0.48 g/cm^3, tapped density: 0.55-0.60 g/cm^3, Carr's index: 11.8%-20%, Hausner's ratio: 1.22-1.25) and post-compression parameters (weight variation: 0.9%-1.6%, hardness: 5.45-5.6kg/cm^2, friability: 0.1%-0.4%, *in vitro* wetting time: 1.44-4.4 minutes, *in vitro* disintegration time: 1.4-4.4 minutes were within acceptable limits. Direct compression formulations exhibited superior dissolution rates, with fold enhancements of 1.22 (BS), 1.23 (SSG), and 1.18 (CCS) compared to wet granulation. Formulations IL4, IL8, and IL12 (8% disintegrant, direct compression) demonstrated optimal dissolution and mechanical properties, making them the final IR layers selected for sustained release (SR) tablet design. These findings support their potential application in fever management in conditions such as COVID-19.

Keywords: Paracetamol, IR layer, SR tablets, Banana Starch (BS), Sodium Starch Glycolate (SSG), Croscarmellose Sodium (CCS).

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INTRODUCTION

Utility of fast dissolving tablets are very high for fast dissolving tablets (FDTs) because of their great disintegration, enhanced dissolution and there by enhanced absorption of water insoluble drugs. Especially, BCS Class 2 drugs are more suitable for designing of fast dissolving tablets and BCS Class 2 drugs with short $t_{1/2}$ are more suitable to design and formulation of FDTs. Mouth dissolving tablets doesn't require water for administration, especially useful for travel medication, as well medicines for prophylactic medication. These two kind of medication is very much beneficial for patients difficult to swallow medication such as children, old people and bed ridden people. These formulations had great patient compliance for maintenance medication/ routine medication and daily supplements/ nutritional supplements, especially. These formulations applicable when rapid onset of action was needed for ailments such as fever, cold, cough, motion sickness, pains- muscular, tooth, joint and angina pain etc.[1,2] Paracetamol used in different managements such as pain management, fever management and etc because of it's pharmacological category- Non-steroidal anti-inflammatory drug. This work was intended to design IR layer for paracetamol sustained release (SR) tablets with the help of banana starch as natural disintegrating agent, and to compare this layer with IR layers prepared with the use of CCS and SSG, synthetic disintegrating agents. As well to select best IR layers for designing of paracetamol SR tablets. The IR layer was fixed to formulate as 400 mg paracetamol tablet that consists of 300 mg therapeutic paracetamol dose. To get IR layer with high dissolution of paracetamol, two methods were employed namely direct compression and wet granulation. Where direct compression method enables rapid disintegration of tablet and releases paracetamol in rapid rate to produce onset of action in a short time and raises paracetamol concentration to therapeutic level. And IR layer prepared by wet granulation may also get disintegrate very rapidly because of enhance porosity of tablets due to granule have spherical shape, that enables more porosity due to high inter particular spaces enables permeation of dissolution fluid through these pores and rapidly disintegrates the tablet and there by dissoluble rapidly, as well raises paracetamol concentration to the therapeutic level.[3,4] Among all IR layers best IR layers to e selected to design paracetamol SR tablets from this work, and best IR layers to be selected based on *in vitro* evaluation parameters like *in vitro* wetting time, *in vitro* disintegrating time, and *in vitro* dissolution.

MATERIALS

Paracetamol, BS, SSG, CCS, MCC and Talc. All materials gifted by SK. Heleath Care Private Limited, Bolaram, Hyderabad.

METHODS

UV Spectroscopic quantification of paracetamol

*Author for Correspondence: chsphanikumar@gmail.com

Table 1: Formulation table for paracetamol 300 mg IR tablet by direct compression

Ingredient	Pure Drug	IL1	IL2	IL3	IL4	IL5	IL6	IL7	IL8	IL9	IL10	IL11	IL12
Paracetamol	300	300	300	300	300	300	300	300	300	300	300	300	300
BS	-	8	16	24	32	-	-	-	-	-	-	-	-
SSG	-	-	-	-	-	8	16	24	32	-	-	-	-
CCS	-	-	-	-	-	-	-	-	-	8	16	24	32
MCC	92	84	76	68	60	84	76	68	60	84	76	68	60
Mg. stearate	4	4	4	4	4	4	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4	4	4	4	4	4	4
Tablet weight	400	400	400	400	400	400	400	400	400	400	400	400	400

Table 2: Formulation table for paracetamol 300 mg IR tablet by wet granulation technique

Ingredient	IL13	IL14	IL15	IL16	IL17	IL18	IL19	IL20	IL21	IL22	IL23
Paracetamol	300	300	300	300	300	300	300	300	300	300	300
Lactose	50	50	50	50	50	50	50	50	50	50	50
Extra-granular Lactose	34	26	18	10	34	26	18	10	34	26	18
BS	8	16	24	32	-	-	-	-	-	-	-
SSG	-	-	-	-	8	16	24	32	-	-	-
CCS	-	-	-	-	-	-	-	-	8	16	24
Mg. stearate	4	4	4	4	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4	4	4	4	4
Tablet weight	400	400	400	400	400	400	400	400	400	400	400

Paracetamol quantification in pH1.2 gastric simulation fluid (GSF) was performed using a UV Spectroscopic method by constructing a calibration curve. A 1000 µg/ml solution was prepared initially by solubilizing ten mg of paracetamol in ten ml of GSF in a ten ml of volumetric flask (VF), and from this one ml was withdrawn, which was diluted to ten ml VF with GSF to get 100 µg/ml solution. From 100 µg/ml solution, serial dilutions of 0.2 ml to 1.6 ml performed with GSF to ten ml for achieving 2 µg/ml to 16 µg/ml concentrations. The wavelength of maximum absorbance was identified, and absorbance values were recorded for all solutions. A calibration curve plotted with concentration on X-axis and absorbance on Y-axis, and linearity was confirmed by calculating the correlation coefficient (R^2). This validated the method's reliability for paracetamol analysis.

Table 3: Linearity curve values for paracetamol in GSF

Concentration (µg/ml)	Absorbance
2	0.109
4	0.218
6	0.328
8	0.437
10	0.547
12	0.656
14	0.765
16	0.875

Formulation of Paracetamol IR Tablets (Layer)

Formulation of Paracetamol IR Tablets by direct compression technique (Formulation design was showed in Table 1). Paracetamol IR tablets were designed by considering 300 mg of paracetamol as Immediate dose, BS as natural disintegrating agent, CCS & SSG as natural disintegrating agents, and each disintegrating agent was used at four different concentrations such as 2%, 4%, 6% and 8% by weight per tablet. Microcrystalline cellulose (Mg. stearate) was used as directly compressible vehicle i.e. diluent because of its great compaction properties and Magnesium stearate as lubricant at 1% weight per tablet, as well talc as glidant at 1% weight per tablet. A total of 13 formulations designed for direct compression method, where Pure drug formulation was designed without disintegrating agent to evaluate the effect of other formulations with disintegrating agents, by comprehensive study with this formulation. IL1, IL2, IL3 & IL4 formulations were designed with the use of BS as natural disintegrating agent at 2, 4, 6 and 8% by weight per tablet concentrations, IL5, IL6, IL7 & IL8 formulations were designed with the use of SSG, as synthetic disintegrating agent at 2, 4, 6 and 8% by weight per tablet concentrations, and IL9, IL10, IL11 & IL12 formulations were prepared with the use of CCS, as synthetic disintegrating agent at 2, 4, 6 and 8% by weight per tablet concentrations.

The procedure for preparation of paracetamol IR tablets was as followed- initially, required quantity of paracetamol (drug) and microcrystalline cellulose (diluent) and disintegrating agent (BS or SSG or CCS) were passed through sieve number 60 separately and loaded to an empty poly bag and mixed for two minutes. Then, Mg. stearate and talc were sifted using sieve number 40 separately, and loaded to poly bag and mixed all the contents for two minutes. After conformation of good flow properties of all IR tablet mixture by subjecting to pre-

Table 4: Pre-compression evaluarion parameters for paracetamol 300 mg IR Tablets

Formulation Code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's Index (%)	Hausner's ratio
IL1	0.45	0.55	18.18	1.22
IL2	0.46	0.57	19.30	1.24
IL3	0.47	0.58	18.97	1.23
IL4	0.48	0.60	20.00	1.25
IL5	0.45	0.56	19.64	1.24
IL6	0.46	0.57	19.30	1.24
IL7	0.47	0.58	18.97	1.23
IL8	0.48	0.59	18.64	1.23
IL9	0.45	0.56	19.64	1.24
IL10	0.46	0.57	19.30	1.24
IL11	0.47	0.58	18.97	1.23
IL12	0.48	0.59	18.64	1.23
IL13	0.45	0.55	18.18	1.22
IL14	0.46	0.57	19.30	1.24
IL15	0.47	0.58	18.97	1.23
IL16	0.48	0.59	18.64	1.23
IL17	0.45	0.56	19.64	1.24
IL18	0.46	0.57	19.30	1.24
IL19	0.47	0.58	18.97	1.23
IL20	0.48	0.59	18.64	1.23
IL21	0.45	0.56	19.64	1.24
IL22	0.46	0.57	19.30	1.24
IL23	0.47	0.58	18.97	1.23
IL24	0.48	0.59	18.64	1.23

compression evaluation, a tablet weight (400 mg) of IR tablet mixture was weighed individually and compressed as tablet using 16 mm x 9 mm oblong punches in a 16-station Cadmach compression machine.[7,8] After compressing IR tablet they are subjected to post-compression evaluation parameters. Formulation of Paracetamol IR Tablets by wet granulation technique (Showed in Table 2).

Tablets were designed by considering 300 mg of paracetamol as drug for all IR tablets prepared by wet granulation. Lactose was selected as diluent due to its great binding characteristics, Mg. stearate & Talc as lubricant and glidant. Concentrations of all excipients were used as such IR tablets prepared by direct compression method. But excipients are divided as extra-granular and intra-granular ingredients, where paracetamol & lactose were used as intra-granular agents and remaining were used as extra-granular agents. A total of 12 formulations designed for wet granulation method, where IL13, IL14, IL15 & IL16 formulations were designed with the use of BS as natural disintegrating agent at 2, 4, 6 and 8% by weight per tablet concentrations, IL17, IL18, IL19 & IL20 formulations were designed with the use of SSG, as synthetic disintegrating agent at 2, 4, 6 and 8% by weight per tablet concentrations, and IL21, IL22, IL23 & IL24 formulations were prepared with the use of CCS, as synthetic disintegrating agent at 2, 4, 6 and 8% by weight per tablet concentrations (The formulation codes were given in above Table 2). The procedure preparation of paracetamol IR tablets was as followed- paracetamol (drug) and some part of lactose were taken into mortar and prepared a dough mass with the help of water. Dough mass was sifted by sieve number 20 to get the granules, and to remove the moisture and to dry the granules they are kept in hot air oven for one hour, sifted by sieve number 22, and finally placed in a poly bag. Disintegrating agent (BS or SSG or CCS), Mg. stearate and talc were sifted by sieve #40 separately, and all these ingredients loaded to poly bag with granules, and mixed for two minute. The pre-compression parameters were tested and after conformation of good flow properties of all IR tablet mixture they are compressed as tablets by weighing a tablet weight (400 mg) of each tablet mixture, and compressed as a tablet using 16-station Cadmach compression machine using 16 mm x 9 mm oblong punches.[9,10] After compressed as tablets each IR tablet batch was subjected to post-compression evaluation. And procedures for pre-compression and post-compression parameters as followed given below (List of ingredients and quantities were given in Table 2).

Evaluation of paracetamol 300 mg IR tablets (Layers)

Pre-compression parameters (Results were showed in Table 4)

Bulk density

A 10 ml measuring cylinder (V) was weighed, and its weight was noted as W_1. It is filled with paracetamol IR tablet powder mix and weight was noted as W_2. The bulk density for paracetamol IR tablet powder mix was calculated by following equation.[11,12]

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

Tapped density

A 10 ml measuring cylinder (V) was weighed and weight was noted as W_1. It is filled with paracetamol IR 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.[13,14] Tapped density of paracetamol IR tablet mix is calculated by following equation,

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

Carr's consolidation index

Carr's consolidation index is calculated for paracetamol IR tablet mixtures by.[15]

Carr's consolidation index = {[(Tapped density - Bulk density)/Tapped density] x 100}

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

Hausner's Ratio

Hausner's ratio is calculated for paracetamol IR tablet powder mixtures by[16].

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

Acceptance criteria for paracetamol IR 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 IR tablet

Table 5: Post-compression evaluation parameters for paracetamol 300 mg IR Tablets (Layer)

Formulation Code	Weight variation (%)	Hardness (kgs/cm^2)	Friability (%)	Dis-integration time(min.)	Wetting time (min.)
IL1	1.4	5.5	0.49	4.4	3.9
IL2	1.3	5.6	0.38	3.9	3.4
IL3	1.1	5.5	0.29	3.4	3.1
IL4	0.9	5.7	0.21	2.9	2.9
IL5	1.3	5.6	0.48	2.4	2.2
IL6	1.4	5.7	0.39	1.9	1.8
IL7	1.2	5.5	0.28	1.7	1.5
IL8	0.9	5.8	0.19	1.6	1.2
IL9	1.4	5.6	0.51	2.9	2.8
IL10	1.3	5.9	0.38	2.6	2.1
IL11	1.1	5.7	0.31	2.1	1.7
IL12	1	5.7	0.21	1.6	1.1
IL13	1.6	5.5	0.52	4.4	4
IL14	1.3	5.6	0.39	3.9	3.5
IL15	1.1	5.5	0.32	3.6	3
IL16	0.9	5.8	0.23	2.9	2.8
IL17	1.4	5.7	0.49	2.6	2.1
IL18	1.3	5.6	0.38	2.1	1.7
IL19	0.9	5.7	0.29	2	1.5
IL20	1.1	5.6	0.22	1.4	1.1
IL21	1.6	5.8	0.49	2.9	2.7
IL22	1.1	5.3	0.38	2.6	2.1
IL23	0.9	5.7	0.29	2.1	1.6
IL24	1.1	5.6	0.19	1.6	1.1

Table 6: *In vitro* dissolution data for direct compression method

Time (minutes)	Pure Drug	IL1	IL2	IL3	IL4	IL5	IL6	IL7	IL8	IL9	IL10	IL11	IL12
0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	12.48	16.99	18.07	17.30	21.46	19.04	23.99	24.08	26.79	23.49	25.36	27.14	29.98
10	28.76	29.04	31.58	33.46	36.59	34.98	36.48	38.70	41.54	35.33	37.01	38.90	43.04
15	42.83	42.39	45.58	47.62	50.24	48.31	50.12	52.23	55.34	49.45	52.56	54.69	58.78
20	56.68	57.83	60.93	62.78	65.12	62.29	65.37	67.49	70.54	62.61	65.72	68.81	72.94
25	71.29	72.02	75.85	77.75	80.40	77.56	80.58	82.65	85.69	74.33	78.11	81.15	85.14
30	80.94	87.04	90.09	92.50	95.64	92.87	95.74	97.34	100.00	89.69	92.31	95.89	98.99

Table 7: *In vitro* paracetamol dissolution data for wet granulation method

Time (minutes)	Pure Drug	IL13	IL14	IL15	IL16	IL17	IL18	IL19	IL20	IL21	IL22	IL23	IL24
0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	12.48	12.36	14.64	16.36	18.12	18.25	20.39	22.48	24.19	16.18	18.89	20.97	22.74
10	28.76	25.52	27.31	30.63	32.16	30.09	33.56	35.49	38.46	28.01	30.85	33.66	36.44
15	42.83	38.94	42.21	45.49	48.89	45.79	48.25	50.06	53.19	42.06	45.43	48.87	50.08
20	56.68	52.85	55.36	58.28	62.94	58.20	62.97	65.80	68.11	55.41	58.26	62.06	65.14
25	71.29	65.74	68.94	72.94	75.59	72.13	75.07	78.98	82.03	68.16	72.49	75.36	78.09
30	80.94	78.64	82.58	85.19	88.02	85.03	88.38	92.86	95.33	82.74	85.55	88.78	92.77

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 angle of repose calculated by[17,18],

Angle of Repose, $\theta = Tan^{-1} [2h/D]$

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

Post-compression evaluation parameters (Results were showed in Table 5, 6 & 7)

Weight variation

A random sampling of 20 tablets was conducted, and the mass of each individual tablet is determined, and mean mass was then assessed from these individual values. Subsequently, the mass deviation was assessed by comparing the individual mass of each tablet to the mean mass, utilizing a predetermined formula to quantify the degree of variation.[19,20]

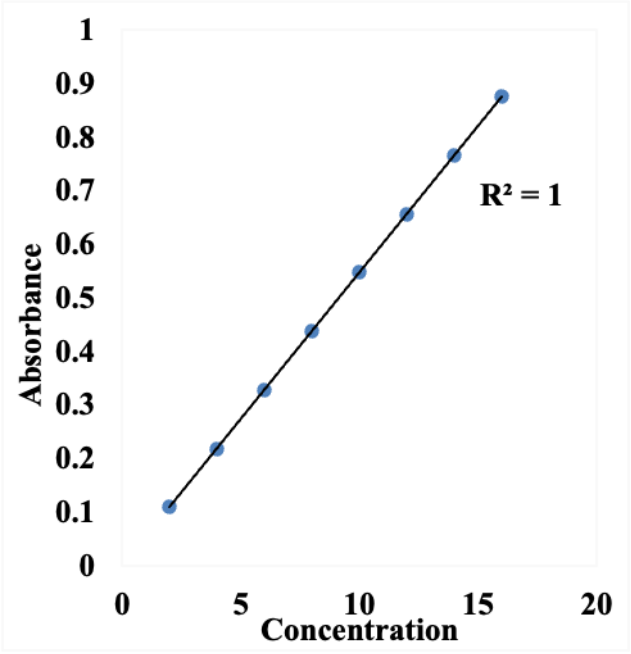

Figure 1: Standard calibration curve values for paracetamol in acid buffer

Weight variation (%) = { [(Individual weight-Mean weight) /Mean weight] x 100}

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

Hardness test

A randomized selection of five tablets from each batch of IR tablets was evaluated for mechanical strength using pharmaceutic hardness tester (Monsanto), with an acceptable limits of ±5%.[21,22]

Friability test

Ten tablets were picked randomly of each batch of paracetamol IR tablets, weight was measured and considered as initial weight, W_1, and tablets were placed in Kshitij friability apparatus and rotated for four minutes at 25 rpm speed, 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. By considering W_1 & W_2 values following formula is used to calculate % friability.

% Friability ={ $[(W_1-W_2)/(W_1)]$ x 100}

The acceptance criteria for all IR tablets was % friability should be <1% for all paracetamol IR tablets.[23,24]

***In vitro* disintegration**

Randomly six paracetamol IR tablets from each batch and placed in six tubes of Kshitij Lab Disintegration apparatus and observed the time taken for disappearance of whole mass of tablet from the bottom of tube covered with sieve number 10 and tube was reciprocated with 25-32 times per minute in one liter GSF maintained at 37±0.5℃, and average time for six tablets was considered as disintegration time for each paracetamol IR tablets. Acceptance criteria was tablets of every batch should disintegrate with in 15 minute.[25,26]

***In vitro* wetting time**

Randomly six paracetamol IR tablets from each batch and place them in six different petri dishes each covered with a layer of filter paper. Place six ml of water on filter paper and observed time taken to wet the tablet visibly. And considered average of six tablets wetting time as an *in vitro* wetting time for each batch of paracetamol IR tablets.[27,28]

***In vitro* dissolution Test**

Randomly six paracetamol IR tablets from each batch and placed in 900 ml GSF maintained at 37±0.5℃ temperature and agitated by 50 rpm using paddle (USP Apparatus II). Samples of 5 ml were collected and replaced with an equivalent volume of GSF at specified time intervals, as presented in Table 6 & 7.Samples were diluted preporely and evaluated using Lab India Double Beam UV-Spectro Photo meter at 243 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 IR tablets and grounded finely and one tablet weight of powder was picked from mortar and solubilized in GSF by sonication, samples were diluted preporely and evaluated using Lab India Double Beam UV-Spectro Photo meter at 243 nm and evaluated % assay using follow equitation[31-45] 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%.

RESULTS AND DISCUSSION

UV Spectroscopic quantification of paracetamol

Linearity curve for Paracetamol in acid buffer (Results were showed in Table 3). The observed λ_{max} for paracetamol in GSF was 243 nm, which was the same standard value for paracetamol in acid buffer i.e. 243 nm. Hence it was identified and confirmed that the drug analysed by the UV-Spectro photo meter was Paracetamol. From the Table 3 & Figure 1, it was observed that the R^2 value for linearity curve for paracetamol in GSF was observed to be 0.999 at concentration range between 2 to 16 µg/ml, measured at 243 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. Pre-compression Parameters (Results were showed in Table 4). As per findings in Table 4, the pre-compaction characteristics of all the paracetamol IR tablet mixtures was found to be as follows- bulk density values ranging 0.45 to 0.48 g/cm^3, tapped density values ranging from 0.55 to 0.60 gm/cm^3. Furthermore, Carr's Index values & Hausner's ratio values ranging from 1.18 to 20% and 1.22 to 1.25. The inferences for above observations are as follows- low bulk density of all tablet powder mixtures from IL1 to IL24 indicates good flow properties and great compactness. A high tapped density compared to bulk

Table 8: *In vitro* pharmacokinetic data for paracetamol 300 mg IR formulations (IL1-IL24)

Formulation Code	Zero-order (R^2)	First-order ($R^{2)}$	Higuchi (n)	Korsmeyer-Peppas (n)
IL1	0.999	0.963	0.915	0.995
IL2	0.999	0.956	0.925	0.998
IL3	0.999	0.938	0.927	0.999
IL4	0.996	0.957	0.941	0.998
IL5	0.998	0.947	0.934	0.999
IL6	0.994	0.975	0.943	0.989
IL7	0.993	0.964	0.949	0.995
IL8	0.989	0.966	0.959	0.995
IL9	0.991	0.968	0.954	0.992
IL10	0.988	0.967	0.960	0.991
IL11	0.986	0.969	0.963	0.989
IL12	0.979	0.965	0.974	0.993
IL13	0.999	0.963	0.907	0.999
IL14	0.999	0.949	0.916	0.999
IL15	0.998	0.951	0.929	0.999
IL16	0.996	0.949	0.939	0.998
IL17	0.998	0.945	0.934	0.996
IL18	0.995	0.937	0.946	0.998
IL19	0.994	0.899	0.947	0.995
IL20	0.992	0.876	0.956	0.997
IL21	0.999	0.941	0.921	0.997
IL22	0.997	0.939	0.935	0.996
IL23	0.995	0.929	0.947	0.997
IL24	0.994	0.891	0.949	0.996

density indicates good compressibility for all mixtures, a good characteristic for tableting. Carr's index and Hausner's ratio values of entire tablet mixes fell within acceptable limits, indicating good flow properties. Consequently, all the powders were suitable for compression into tablets.

Post-compression evaluation parameters (Results were showed in Table No.5)

Findings of post-compaction findings are presented in Table5, revealed that entire paracetamol IR tablets from IL1 to IL24 exhibited the following characteristics: weight variation ranged from 0.9 6% to 1.6%, hardness ranged from 5.3 kg/cm^2 to 5.9 kg/cm^2, friability ranged from 0.19% to 0.52%, *in vitro* wetting time ranged from 1.1 to 4 minutes, and *in vitro* disintegration time ranged from 1.4 to 4.4 minutes. The observations from post-compression parameters of all tablet formulations from IL1 to IL4 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. *In vitro* wetting time indicates all tablets able and capable of absorbing water for rapid disintegration and disintegration values indicates that, all tablets were having rapid disintegration to enhance the dissolution. This study demonstrates a strong relationship among wetting time disintegration time, indicating that quicker tablet wetting may facilitate faster disintegration, thereby improving the dissolution process. (As showed in Table 5).

***In vitro* dissolution studies**

Direct compression method (Results were showed in Table 6). As per the findings showed in Table 6, the Pure drug formulation was releasing nearly 81% of drug at the end of 30th minute and formulation designed with BS-IL1, IL2, IL3 and IL4 were releasing more than pure drug formulation (formulation with out disintegrating agent) i.e. nearly 87 %, 91%, 93% and 96%. Hence, it was observed to be BS has ability to enhance dissolution of paracetamol by its disintegrating effect, at maximum BS is enhancing paracetamol dissolution to 1.18 fold. Among all formulations designed with BS IL4 (8% w/w) was showing high dissolution, and ascending order of formulations based on their *in vitro* dissolution were a follows for formulations deigned with BS as disintegrating agent,

Pure Drug < IL1 < IL2 < IL3 < IL4

As per finding showed in Table 6, the formulation designed with SSG-IL5, IL6, IL7 and IL8 were showing dug release more than pure drug formulation (formulation with out disintegrating agent) i.e. approximately 93 %, 96%, 97% and 100%. Hence, it was observed to be SSG has ability to enhance dissolution of paracetamol by its super disintegrating effect, at maximum SSG is enhancing paracetamol dissolution to 1.23 fold. Among all SSG formulations IL8 (8% w/w) was showing high dissolution, and ascending order of formulations based on their *in vitro* dissolution were a follows for formulations deigned with SSG as disintegrating agent,

Pure Drug < IL5 < IL6 < IL7 < IL8

As per finding showed Table 6, it was observed that Pure drug formulation was releasing nearly 81% of drug at the end of 30th minute and formulation designed with CCS-IL9, IL10, IL11 and IL12 were releasing more than pure drug formulation (formulation with out disintegrating agent) i.e. nearly 87 %, 92%, 96% and 99%. Hence, it was observed to be CCS has ability to enhance dissolution of paracetamol by its disintegrating effect, at maximum CCS is enhancing paracetamol dissolution to 1.22 fold. Among all formulations designed with CCS IL12 (8% w/w) was showing high dissolution, and ascending order of formulations based on their *in vitro* dissolution were a follows for formulations deigned with CCS as disintegrating agent,

Pure Drug < IL9 < IL10 < IL11 < IL12

Wet granulation method (Results were showed in Table 7). As per findings showed in Table 7, it was observed that Pure drug formulation was releasing nearly 81% of drug at the end of 30th minute and formulation designed with BS-IL13, IL14, IL15 and IL16 were releasing more than pure drug formulation (formulation with out disintegrating agent) except IL13 i.e. nearly 79 %, 83%, 85% and 88%. Hence, it was observed to be BS has ability to enhance dissolution of paracetamol by its disintegrating effect, at maximum BS is enhancing paracetamol dissolution to 1.09 fold. Among all formulations designed with BS IL16 (8% w/w) was showing high dissolution, and ascending order

of formulations based on their *in vitro* dissolution were a follows for formulations deigned with BS as disintegrating agent,

IL13 < Pure Drug < IL14 < IL15 < IL16

All these formulations were prepared with the help of wet granulation method.

From the Table 7, it was observed that, the formulation designed with SSG-IL17, IL18, IL19 and IL20 were showing dug release more than pure drug formulation (formulation with out disintegrating agent) i.e. nearly 85%, 88%, 93% and 95%. Hence, it was observed to be SSG has ability to enhance dissolution of paracetamol by its super-disintegrating effect, at maximum SSG is enhancing paracetamol dissolution to 1.18 fold. Among all SSG formulations IL20 (8% w/w) was showing high dissolution, and ascending order of formulations based on their *in vitro* dissolution were a follows for formulations deigned with SSG as disintegrating agent,

Pure Drug < IL17 < IL18 < IL19 < IL20

From Table 7, it was observed that the pure drug formulation released approximately 81% of the drug at the end of the 30th minute. In comparison, formulations designed with CCS-IL21, IL22, IL23, and IL24-released higher percentages than the pure drug formulation (which lacked a disintegrant), with drug release values approximately 83%, 85%, 89%, and 93%, respectively. Hence, it was observed to be CCS has ability to enhance dissolution of paracetamol by its disintegrating effect, at maximum CCS is enhancing paracetamol dissolution to 1.15 fold. Among all formulations designed with CCS IL24 (8% w/w) was showing high dissolution, and ascending order of formulations based on their *in vitro* dissolution were a follows for formulations deigned with CCS as disintegrating agent,

Pure Drug < IL21 < IL22 < IL23 < IL24

Finally, from *in vitro* dissolution findings it was observed that, paracetamol IR tablets tableted from direct compression technique were having high dissolution compared to the wet granulation technique. Basically, tablets with high disintegrating agent concentration (8% w/w) have showed high dissolution against other concentrations. Especially, tablets prepared by direct compression method with high disintegrating agent were showing great dissolution compared to wet granulation method. Hence, paracetamol IR tablet prepared with direct compression method was preferred to select as IR layers for designing of paracetamol SR tablets. And tablet designed with synthetic disintegrating agents (SSG and CCS) have showed high dissolution compared to natural disintegrating agent (BS), and their ascending order of dissolution as follows,

IL4 (96%) < IL12 (99%) < IL8 (100%)

Hence, these three IR layers were selected for deigning paracetamol SR tablets. Where, IL4 was designed with BS, IL8 designed with SSG and IL12 designed with CCS as disintegrating agents. These three layers were prepared with the help of three different disintegrating agents and were showing approximately 100% drug release at the end of 30th minute.

Pharmacokinetic data (Results were showed in Table 8)

An examination of Table 8 revealed that the correlation coefficient for zero-order release profile spanned from 0.997 to 0.999, where as those for first order profiles ranged from 0.876 to 0.975. The release exponent (n) values derived from Higuchi plots fell within the range of 0.907 to 0.974, while those obtained from Korsmeyer-Peppas plots ranged from 0.989 to 0.999. Based on the *in vitro* dissolution data, it was evident that the release kinetics of the drug from all IR tablets confirmed predominantly to zero-order kinetics. The underlying mechanism governing drug release was characterized by non-Fickian diffusion, indicative of anomalous transport phenomena.

CONCLUSION

The current research work was conducted to select best IR layer for preparation of paracetamol SR tablets for fever management in infection such as Covid-19, dengue and etc. For this BS was chosen as natural disintegrating agent and compared with synthetic disintegrating agents SSG and CCS. Four concentrations of each disintegrating agent were elected and evaluated for best and rapid *in vitro* dissolution, because IR layer upon disintegration and dissolution raises paracetamol concentration to therapeutic level, and this is significant step in eliciting of onset of action. Hence, two methods, namely direct compression and wet granulation,were employed for a comprehensive evaluation and comparison of *in vitro* dissolution between the two approaches. Finally, it was found from *in vitro* dissolution studies that direct compression method was best suited to design IR layers with improved dissolution, this was evaluated by comparing *in vitro* dissolution with formulation with out disintegrating agent and found formulations prepared with direct compression have enhanced *in vitro* dissolution of paracetamol to a maximum of 1.23 fold and wet granulation were to only 1.18 fold. Hence, the direct compression method was selected as the optimal approach for preparing paracetamol IR layers. When, considering disintegrating agents, all three disintegrating agents (BS, SSG & CCS) were showing increased *in vitro* dissolution with increase disintegrating agent concentration, i.e. at 8% w/w concentration they are showing highest *in vitro* dissolution. synthetic disintegrating agent (SSG) was showing high *in vitro* dissolution compared to natural disintegrating agent (BS). Though, the synthetic disintegrating agents were showing great dissolution compared to BS, BS also considered as disintegrating agent because the fold of increment of paracetamol was differed with synthetic agent (SSG) was only 1.01. Hence, IR layers designed at 8% W/W per tablet, specifically prepared by direct compression were considered as final selected layers for designing of paracetamol SR tablets. The final selected IR layers were IL4, IL8 and IL12, all layers consists of 300 mg paracetamol dose, the order of release from these The IR layers exhibited zero-order kinetics, characterized by a non-Fickian, anomalous transport mechanism.

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