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DEVELOPMENT AND EVALUATION OF A DIRECTLY COMPRESSIBLE CO-PROCESSED MULTIFUNCTION SUSTAINED RELEASE AGENT FOR ISOSORBIDE MONONITRATE SUSTAINED RELEASE TABLETS

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ABSTRACT

Directly compressible co-processed sustained release multifunction agent [DCCSRA] comprising povidone and glyceryl behenate in the ratio of 1:1, 1:2 and 1:3 were prepared and evaluated for formulation of sustained release tablets of isosorbide mononitrate. The DCCSRA exhibited good flow and compressibility. The DCCSRA, prepared by hot melting method and co-precipitation method served as a retardant, binder and lubricant in isosorbide mononitrate sustained release tablets. The DCCSRA may be used for manufacturing of isosorbide mononitrate sustained release tablets.

INTRODUCTION: Co-processed excipients are combinations of two or more excipients that possess performance advantages when compared to a physical mixture of the same combination of excipients. Typically co-processed excipients are produced using some form of specialized manufacturing process and are helpful in achieving the desirable characteristics in a formulation [1-7]. This work focuses on the preparation and evaluation of a co-processed excipient comprising povidone and glyceryl behenate. This co-processed excepient is useful as a sustained release matrix forming agent. Glyceryl behenate is mainly used as tablet and capsule lubricant and as tablet binder. It has been used in preparation of sustained release tablets and as matrix-forming agent (above 10 % w/w) for the controlled release of water soluble drugs.

Povidone is used as binder (at a concentration of 0.5% w/w to 5 % w/w) in tablets. It also acts as a solubilizer and enhances the dissolution of poorly soluble drugs from solid dosage forms. The molecular adduct formation of povidone may be used to advantage in slow release solid dosage forms [8]. The co-processing of glyceryl behenate with povidone by hot melting method and co- precipitation method leads to formation of a multifunctional excipient which can act as a matrix forming agent, binder and lubricant. This improved functionality of the co-processed excipient may reduce the time and cost of manufacture of sustained release tablets. Since povidone is hydrophilic, the hydrophobicity of glyceryl behenate gets reduced when co-processed with povidone. To check the retention capacity of the DCCSRA, the drug molecule selected need to have a high solubility. For this study, Isosorbide mononitrate was selected as a model drug based on this solubility criterion.

MATERIALS AND METHODS:

Materials: Glyceryl Behenate (Compritol 888), Povidone K 25, Dicalcium Phosphate Dihydrate (Emcompress), Lactose Monohydrate (Flowlac 100) and diluted Isosorbide mononitrate were received from Micro Labs Ltd. (Bangalore, India).

Methods: The following experimental approach has been used in this work.

- Preparation of physical blend of glyceryl behenate and povidone and evaluation of its flow property.
- Preparation of DCCSRAs mixtures of glyceryl behenate and povidone comprising different ratios of the two components by hot melting method and co-precipitation method and evaluation of the flow of the DCCSRAs.
- Preparation of the Isosorbide mononitrate sustained release tablets using the DCCSRAs.
- Evaluation of the Isosorbide mononitrate release pattern from tablets prepared with DCCSRAs and comparison of the release data with that of reference product [Imnit 60 tablets]

The flow characteristic of the physical blend of glyceryl behenate and povidone has been compared with that of the co-processed excipient. The co-processed excipient was evaluated for its suitability for direct compression of isosorbide mononitrate sustained release tablets.

Preparation of Physical Blend of Glyceryl behenate and Povidone: Povidone and glyceryl behenate were blended in the ratio of 1:1, 1: 2 and 1: 3 in a lab scale double cone blender.

Preparation of Directly compressible co-processed sustained release multifunctional

agents by Hot melting Method [DCCSRA-HM]: DCCSRA-HMs was prepared by hot melting method. Glyceryl behenate and povidone were passed through 40-mesh sieve and mixed well. This powder mix was transferred into a stainless steel vessel and heated to about 90°C in a water bath with stirring until a smooth paste was formed. In this mix glyceryl behenate melts since its melting range is between 65-77°C. This mass was then cooled to room temperature with intermittent mixing. The mass was then milled in a multimill with 1.5mm screen and passed through 30-mesh sieve and stored in an airtight container till further use. The ratios of the components in the co-processed excipients have been presented in **Table 1**.

Preparation of Directly compressible co-processed sustained release multifunctional agents by Co-precipitation method [DCCSRA-CM]: DCCSRA-CMs were prepared by co-precipitation method. Glyceryl behenate and povidone were passed through 40-mesh sieve and mixed well. This powder mix (50g) was transferred into a beaker containing methylene chloride (250 ml). The contents of the beaker were stirred using a magnetic stirrer to dissolve the powder mix in methylene chloride.

The temperature was maintained between 40°C and 45°C, and stirring was continued till most of methylene chloride has been evaporated. The wet coherent mass was granulated through 30-mesh sieve. The wet granules were dried in a tray drier at 45°C for 15 minutes. The dried granules were sifted through 30-mesh sieve and stored in an airtight container till further use. The ratios of the components in the co-processed excipients have been presented in **Table 1**.

TABLE 1: DCCSRA – RATIO OF THE COMPONENTS

Hot Melting Method		
Composition		**Ratio**
Composition-I	[DCCSRA-HM-I]	Povidone : Glyceryl Behenate [1:1]
Composition-II	[DCCSRA-HM-II]	Povidone : Glyceryl Behenate [1:2]
Composition-III	[DCCSRA-HM-III]	Povidone : Glyceryl Behenate [1:3]
Co-precipitation method		
Composition-I	[DCCSRA-CM-I]	Povidone : Glyceryl Behenate [1:1]
Composition-II	[DCCSRA-CM-II]	Povidone : Glyceryl Behenate [1:2]
Composition-III	[DCCSRA-CM-III]	Povidone : Glyceryl Behenate [1:3]

Evaluation of Angle of repose:

Angle of repose: For the measurement of angle of repose, a glass funnel was secured with its tip at a given height (H) above a piece of graph paper placed on a horizontal surface. Powder was passed through the funnel until the apex of the conical pile touched through the funnel. The angle of repose was calculated with formula tan $\alpha = H/R$, where α is the angle of repose and R is the radius of the conical pile. The angle of repose of the physical blend and co-processed excipient were measured by the above method. The results have been tabulated in **Table 2**.

TABLE 2: EVALUATION OF FLOW PROPERTY [ANGLE OF REPOSE] FOR THE PHYSICAL BLEND AND DCCSRA

Composition	Angle of Repose		
	Physical Blend	DCCSRA-HM	DCCSRA-CM
Composition-I	40°	23°	21°
Composition-II	42°	25°	23°
Composition-III	45°	28°	26°
Pure Povidone K 25		35°	
Pure Glyceryl behenate		43°	

Preparation and Evaluation of Isosorbide mononitrate sustained release tablets: Isosorbide mononitrate sustained release tablets were prepared by direct compression. Diluted Isosorbide mononitrate, DCCSRA-HM/ DCCSRA-CM and Emcompress / Flowlac 100 were passed through 30 mesh sieve and then blended. The angle of repose of the blends was measured as described above [**Table 2**]. The tablets were compressed with a target weight of 300mg using 9 mm normal concave punches using an 8 station tablet machine (Rimek). The composition of various trial formulations formulated with the DCCSRA has been presented in the **Tables 3** and **4**.

TABLE 3: FORMULATION COMPOSITION OF ISOSORBIDE MONONITRATE SUSTAINED RELEASE TABLETS USING DCCSRA-HM [TRIALS]

Materials	Batch Code						
	HT1	HT2	HT3	HT4	HT5	HT6	HT7
Diluted Isosorbide mononitrate*	75	75	75	75	75	75	75
DCCSRA- HM-I	150						
DCCSRA -HM-II		150					
DCCSRA- HM-III			150	150	60	75	90
Flowlac 100				75			
Emcompress	75	75	75		165	150	135

* Diluted isosorbide 75mg is equivalent to 60 mg of isosorbide mononitrate

TABLE 4: FORMULATION COMPOSITION OF ISOSORBIDE MONONITRATE SUSTAINED RELEASE TABLETS USING DCCSRA-CM [TRIALS]

Materials	Batch Code						
	CT1	CT2	CT3	CT4	CT5	CT6	CT7
Diluted Isosorbide mononitrate*	75	75	75	75	75	75	75
DCCSRA- CM-I	150						
DCCSRA -CM-II		150					
DCCSRA- CM-III			150	150	60	75	90
Flowlac 100				75			
Emcompress	75	75	75		165	150	135

* Diluted isosorbide 75mg is equivalent to 60 mg of isosorbide mononitrate

The tablets were evaluated for crushing strength, friability and in vitro dissolution release. Crushing strength of the tablets was measured using Dr Schleuniger Pharmatron Tablet tester. Friability was evaluated as the percentage weight loss of 20 tablets tumbled in a friabilator (Model EF2, Electrolab, India) for 4 minutes at 25 rpm. The i*n-vitro* drug release study of Isosorbide mononitrate was estimated using a USP dissolution test apparatus (model TDT-08L, Electrolab) fitted with paddle (50 rpm) at 37±0.5°C using 900 ml of water as dissolution medium. The samples of 10 ml volume were withdrawn at 1, 2, 4, 6, 8, 10 & 12 hours and filtered through 0.45µm membrane filter. The Isosorbide mononitrate release was estimated by HPLC method. A mixture of 70 volumes of water and 30 volumes of methanol was used as the mobile phase. A flow rate of 1 ml/minute and a detection wavelength of 220nm were selected for the estimation. A C18, 250mm x 4.6 mm, 5µm HPLC column [GL Sciences -Inertsil ODS 3] was used. The Dionex HPLC system model P680A LPG 4 was used and the data was processed using the Chromeleon software.

Evaluation of reference product of Isosorbide mononitrate sustained release tablets [Imnit 60 tablet]: The *in vitro* dissolution release of the reference product [Imnit 60 tablet] was estimated as described above in different dissolution media.

RESULTS:

Physical properties of glyceryl behenate, povidone K 25 and the physical blend of glyceryl behenate with povidone K 25: The angle of repose of pure glyceryl behenate, pure povidone K 25 and the physical blend have been presented in Table 2. The angle of repose values of the physical blend ranging from 40^{o} to 45^{o} indicates that the flow property of the physical blend may not be suitable for direct compression. The angle of repose values of the DCCSRA-HM and DCCSRA-CM between 21^{o} to 28^{o} indicates that the DCCSRA have a good flow suitable for use in direct compression process [Table 2].

Evaluation of Isosorbide mononitrate tablets compressed with DCCSRA-HMs and DCCSRA-CMs: To investigate the versatility of the DCCSRA-HMs and DCCSRA-CMs, tablets of Isosorbide mononitrate were prepared and evaluated for crushing strength, friability and in vitro dissolution release. Initially batches HT1 to HT3 and CT1 to CT3 were formulated to assess the flow of the blend, lubrication capacity, binding capacity (crushing strength) and the retarding capacity of the DCCSRA-HMs & DCCSRA-CMs. The concentration of Diluted Isosorbide mononitrate was kept constant at 75 mg (25 % w/w) which is equivalent to 60 mg of Isosorbide mononitrate in all the batches. The composition of the DCCSRA-HM and DCCSRA-CM used in the HT1, HT2, HT3, CT1, CT2, CT3 batches has been given in Tables 3 and 4. The concentration of DCCSRA-HM used was 150 mg (50% w/w) in the three batches of HT1 to HT3 and concentration of DCCSRA-CM used was 150 mg (50% w/w) in the three batches of CT1 to CT3. The diluent used in these batches was dicalcium phosphate dihydrate (Emcompress) at a concentration of 75mg (25% w/w) in each batch. The results in Table 2 show that the flow of the DCCSRA is much superior to that of the physical blend of the two components showing that the DCCSRA is suitable for the direct compression process. The crushing strength of the tablets was found to be maximum for tablets compressed with DCCSRA (povidone: glyceryl behenate [1:1]) when compared to the tablets compressed with DCCSRA with lesser quantities of povidone [Tables 5 and 6].

TABLE 5: EVALUATION OF BLEND AND TABLETS OF ISOSORBIDE MONONITRATE COMPRESSED WITH DCCSRA-HM

Parameters	Batch Code						
	HT1	HT2	HT3	HT4	HT5	HT6	HT7
Angle of repose	23°	25°	28°	29°	24°	26°	27°
Crushing strength	100N	95N	85N	85N	85N	85N	85N
Friability	0.06%	0.09%	0.12%	0.14%	0.12%	0.13%	0.12%

TABLE 6: EVALUATION OF BLEND AND TABLETS OF ISOSORBIDE MONONITRATE COMPRESSED WITH DCCSRA-CM

Parameters	Batch Code						
	CT1	CT2	CT3	CT4	CT5	CT6	CT7
Angle of repose	22°	23°	25°	27°	23°	24°	26°
Crushing strength	110N	100N	90N	90N	90N	90N	90N
Friability	0.07%	0.10%	0.13%	0.14%	0.12%	0.13%	0.12%

The *in-vitro* dissolution profile in Figures 1 and 2 show that the dissolution release decreases with increase in the concentration of Glyceryl behenate in the DCCSRA-HM and DCCSRA-CM. The dissolution release from formulations of Isosorbide mononitrate prepared with DCCSRA of different ratios was in the order of 1:1 > 1:2 > 1:3. The release at each time point was highest with excipient of ratio 1:1 and lowest with ratio of 1:3. Refer to the dissolution release values of trials HT1, HT2, HT3, CT1, CT2 and CT3 in Tables 7 and 8.

TABLE 7: DRUG RELEASE ISOSORBIDE MONONITRATE FROM TRIAL FORMULATIONS HT1 TO HT4

Time in Hours	% Mean Drug Release In Water			
	HT1	HT2	HT3	HT4
1	14	11	8	14
2	23	16	12	18
4	31	27	18	23
6	36	30	29	30
8	49	37	32	36
10	56	45	41	45
12	61	52	46	53

TABLE 8: DRUG RELEASE OF ISOSORBIDE MONONITRATE FROM TRIAL FORMULATIONS CT1 TO CT4

Time in Hours	% Mean Drug Release In Water			
	CT1	CT2	CT3	CT4
1	12	10	7	13
2	21	15	11	16
4	29	23	16	21
6	34	28	24	29
8	48	36	31	35
10	55	43	39	44
12	59	49	44	51

Effect of Lactose and Dicalcium Phosphate: The batch HT3 & HT4 were formulated using the DCCSRA-HM [Povidone: Glyceryl behenate: 1:3] and batch CT3 & CT4 were formulated using the DCCSRA-CM [Povidone: Glyceryl behenate: 1:3]. In batches HT3 and CT3 dicalcium phosphate (Emcompress) was used as diluent and in batches HT4 and CT4 Lactose (Flowlac 100) was used as diluent. The dissolution release results of batches HT3 and HT4 have been shown in Figure 1 and Table 7 and the dissolution release results of batches CT3 and CT4 have been shown in Figure 2 and Table 8.

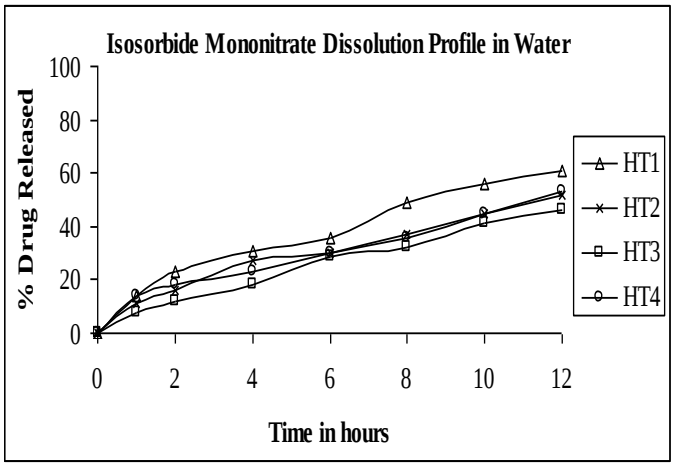

FIG. 1: *IN VITRO* DISSOLUTION RELEASE PROFILE OF BATCHES HT1 TO HT4 IN WATER

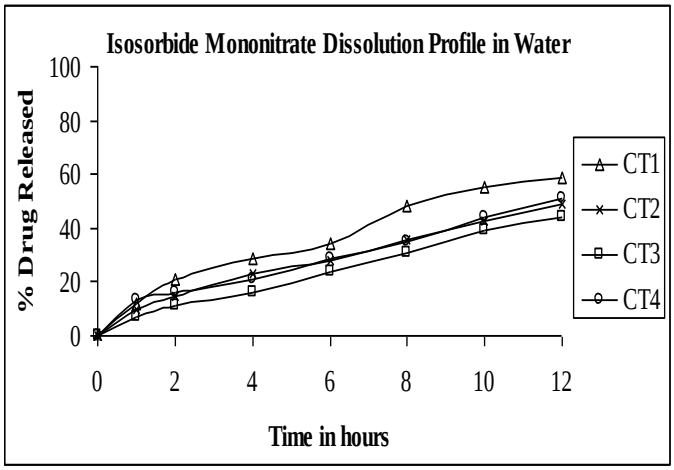

FIG. 2: *IN VITRO* DISSOLUTION RELEASE PROFILE OF BATCHES CT1 TO CT4 IN WATER

Evaluation of Dissolution profile of Reference Product [Imnit 60 tablet] and trial formulations: To match the dissolution profile of test product with that of the reference product, the trial batches of HT5 to HT7 and CT5 to CT7 were formulated by varying the concentration of co-processed multifunctional sustained release agent. The DCCSRA-HM of povidone: glyceryl behenate (1:3) was used for trials HT5 to HT7 and the DCCSRA-CM of povidone: glyceryl behenate (1:3) was used for trials CT5 to CT7. The tablet weight was kept constant at 300 mg and the difference in the concentration of DCCSRA was adjusted with dicalcium phosphate [Emcompress].

The dissolution release of batches HT5 to HT7 and CT5 to CT7 were checked in water as well as dissolution media of three different pH values. The in-vitro dissolution profile results of Imnit 60 tablet [reference product] and trial batches HT5 to HT7 and CT5 to CT7 have been presented in the Figures 3 to 10 and the dissolution release values have been tabulated in Tables 9 and 10.

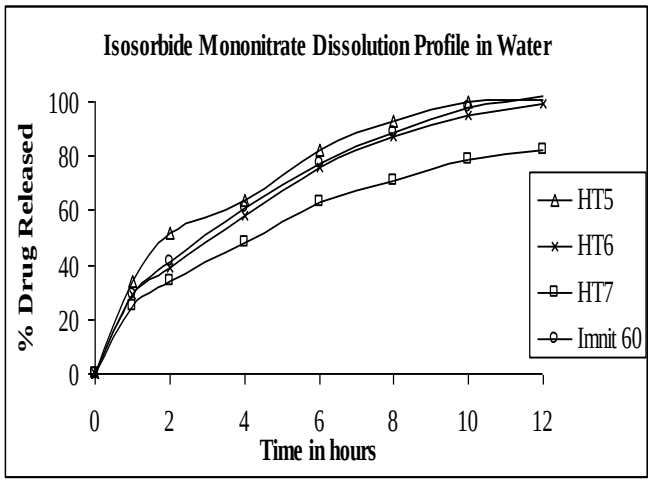

FIG. 3: *IN VITRO* DISSOLUTION RELEASE PROFILE OF IMNIT 60 TABLETS AND TRIAL BATCHES HT5 TO HT7 IN WATER

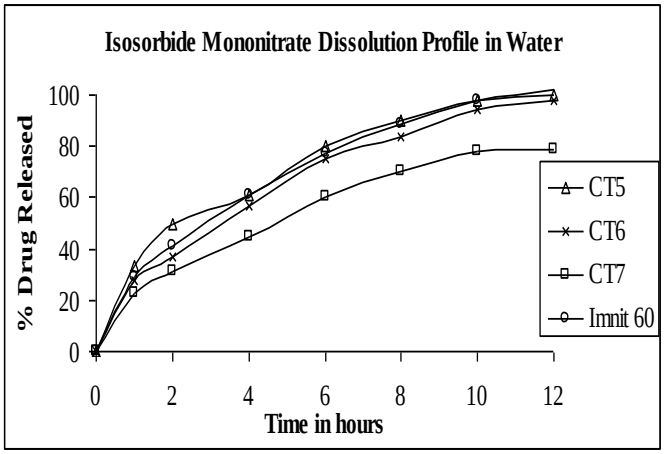

FIG. 4: *IN VITRO* DISSOLUTION RELEASE PROFILE OF IMNIT 60 TABLETS AND TRIAL BATCHES CT5 TO CT7 IN WATER

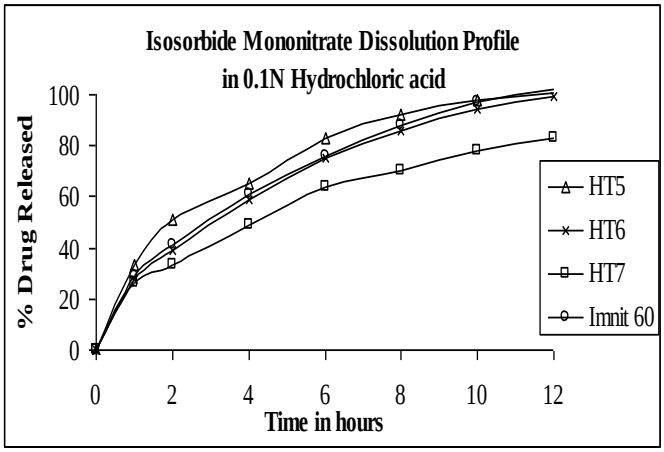

FIG. 5: *IN VITRO* DISSOLUTION RELEASE PROFILE OF IMNIT 60 TABLETS AND TRIAL BATCHES HT5 TO HT7 IN 0.1N HYDROCHLORIC ACID

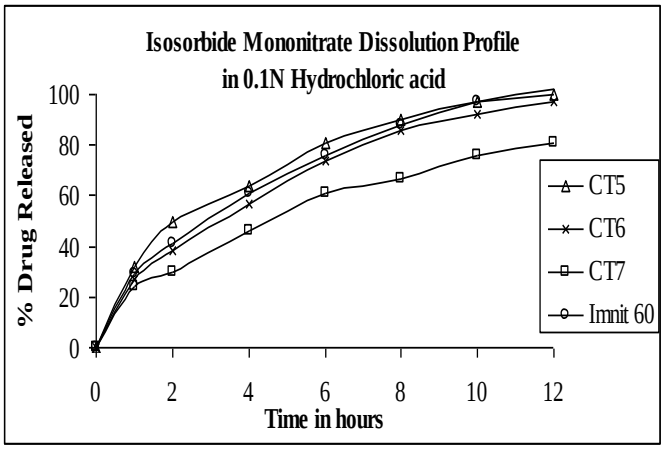

FIG. 6: *IN VITRO* DISSOLUTION RELEASE PROFILE OF IMNIT 60 TABLETS AND TRIAL BATCHES CT5 TO CT7 IN 0.1N HYDROCHLORIC ACID

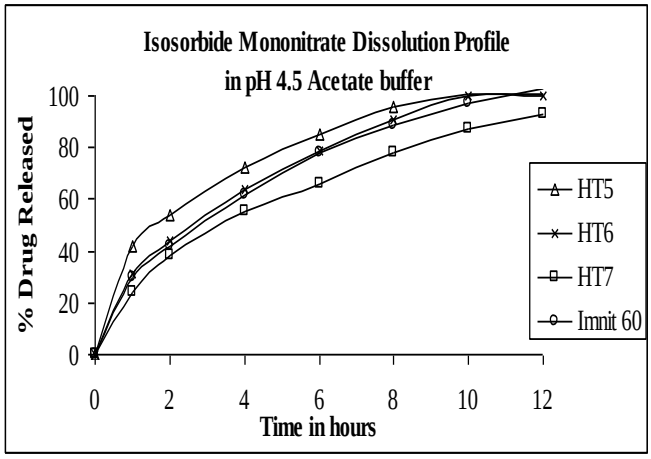

FIG. 7: *IN VITRO* DISSOLUTION RELEASE PROFILE OF IMNIT 60 TABLETS AND TRIAL BATCHES HT5 TO HT7 IN pH 4.5 ACETATE BUFFER

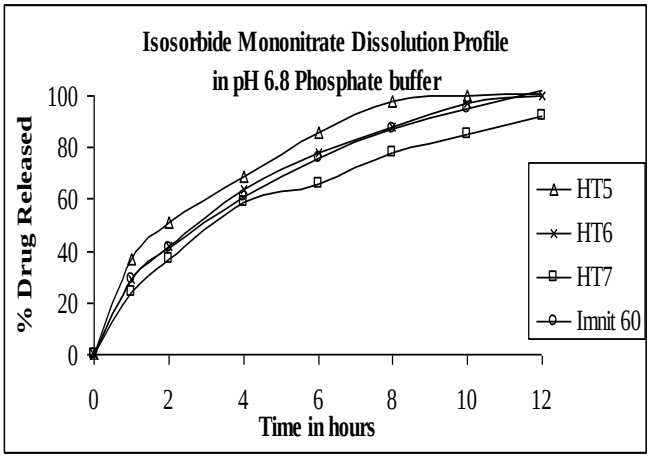

FIG. 9: *IN VITRO* DISSOLUTION RELEASE PROFILE OF IMNIT 60 TABLETS AND TRIAL BATCHES HT5 TO HT7 IN pH 6.8 PHOSPHATE BUFFER

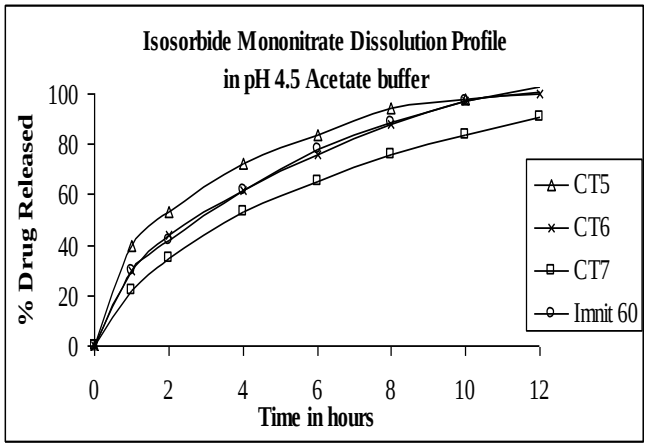

FIG. 8: *IN VITRO* DISSOLUTION RELEASE PROFILE OF IMNIT 60 TABLETS AND TRIAL BATCHES CT5 TO CT7 IN pH 4.5 ACETATE BUFFER

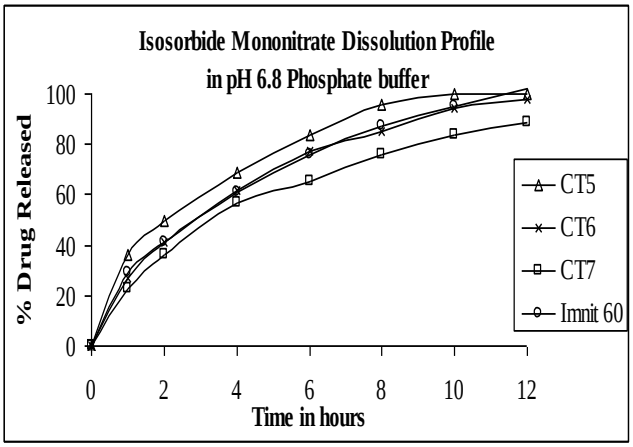

FIG. 10: *IN VITRO* DISSOLUTION RELEASE PROFILE OF IMNIT 60 TABLETS AND TRIAL BATCHES CT5 TO CT7 IN pH 6.8 PHOSPHATE BUFFER

TABLE 9: DISSOLUTION RELEASE VALUES OF TRIALS HT5, HT6, HT7 AND REFERENCE PRODUCT IMNIT-60 TABLET IN DIFFERENT DISSOLUTION MEDIA

Time in Hours	% Mean Drug Release															
	Water				0.1N Hydrochloric acid				pH 4.5 Acetate Buffer				pH 6.8 Phosphate Buffer			
	HT5	HT6	HT7	Imnit	HT5	HT6	HT7	Imnit	HT5	HT6	HT7	Imnit	HT5	HT6	HT7	Imnit
1	34	29	25	29	33	28	26	29	42	31	24	30	37	29	24	29
2	52	39	34	41	51	39	33	41	54	44	38	42	51	42	37	41
4	64	58	48	61	65	59	49	61	72	64	55	62	69	64	59	61
6	82	76	63	77	83	75	64	76	85	79	66	78	86	78	66	76
8	93	87	71	89	92	86	70	88	96	91	78	89	98	88	78	87
10	100	95	79	98	98	94	78	97	101	100	87	97	100	97	85	95
12	101	99	82	102	101	99	83	102	101	100	93	103	101	100	92	102

TABLE 10: DISSOLUTION RELEASE VALUES OF TRIALS CT5, CT6, CT7 AND REFERENCE PRODUCT IMNIT-60 TABLET IN DIFFERENT DISSOLUTION MEDIA

Time in Hours	% Mean Drug Release															
	Water				0.1N Hydrochloric acid				pH 4.5 Acetate Buffer				pH 6.8 Phosphate Buffer			
	CT5	CT6	CT7	Imnit	CT5	CT6	CT7	Imnit	CT5	CT6	CT7	Imnit	CT5	CT6	CT7	Imnit
1	33	28	23	29	32	27	24	29	40	30	22	30	36	27	23	29
2	50	37	31	41	50	38	30	41	53	44	35	42	50	41	36	41
4	61	57	45	61	64	57	46	61	72	62	53	62	69	62	57	61
6	80	75	60	77	81	74	61	76	84	76	65	78	84	77	65	76
8	90	84	70	89	90	86	67	88	94	88	76	89	96	85	76	87
10	98	94	78	98	97	92	76	97	98	97	84	97	100	94	84	95
12	100	98	79	102	100	97	81	102	101	100	91	103	100	98	89	102

DISCUSSION: In the present study the DCCSRAs were prepared and the feasibility of using the co-processed agent as multifunctional agent in a sustained release formulation was evaluated by comparing the in vitro dissolution release of the trial formulations containing isosorbide mononitrate with that of a reference product [Imnit 60 tablet]. The angle of repose of physical blends of povidone K 25 and glyceryl behenate (containing the components in the ratios 1:1,1:2 and 1:3) were found to be 40°, 42° and 45° respectively indicating that the flow of the blend has to be improved if the blend has to be used for direct compression .

The angle of repose of DCCSRA-HMs of povidone K 25 and glyceryl behenate were 23°, 25° and 28° respectively [Tables 1 and 2]. The angle of repose of DCCSRA-CMs of povidone K 25 and glyceryl behenate were 21°, 23° and 26° respectively [Tables 1 and 2]. These angle of repose values show that the DCCSRAs have better flow than the physical blend of povidone and glyceryl behenate. The angle of repose values of the trial formulation blends have been presented in Tables 5 and 6. These values below 30° indicate the good flow of these blends which is suitable for direct compression. The results of crushing strength and friability of trial batch tablets reveal that the co-processed agent provides sufficient strength to the tablets [Tables 5 and 6]. The batches HT3 and CT3 were formulated with dicalcium phosphate (Emcompress) which is an insoluble diluent and the batches HT4 and CT4 were formulated with lactose (Flowlac 100) which is a soluble diluent. The in vitro dissolution release of HT4 and CT4 batches was higher at all the time points when compared with HT3 and CT3 batches [Tables 7 and 8]. This shows that the dissolution release increases when a soluble excipient is used in the formulation along with the proposed DCCSRA.

The f1 and f2 results [**Table 11**] show that the dissolution release pattern of the trial batches HT5 and HT6 and CT5 and CT6 were similar to that of reference product [Imnit 60 tablet]. Among these four batches, the release pattern of HT6 and CT6 was closer to the release pattern of the reference product [Imnit-60 tablet] in all the four dissolution media [9, 10]. The stability data of the trial formulations shown in Tables 12 and 13 indicate that the trial product has a satisfactory stability of up to 6 months in 40°C / 75% RH and at 30°C / 65% RH. The details of analytical methods used for assay, dissolution and related substances test of the trial product have been presented in Table 14.

TABLE 11: RESULTS OF DIFFERENCE FACTOR (F1) AND SIMILARITY FACTOR (F2)

Dissolution Medium	f1 Value						f2 Value					
	HT5	HT6	HT7	CT5	CT6	CT7	HT5	HT6	HT7	CT5	CT6	CT7
Water	6.24	2.82	19.11	3.82	4.83	22.33	63.18	80.29	41.57	69.33	71.02	38.72
0.1N hydrochloric acid	6.28	2.83	18.42	4.86	4.66	22.06	63.28	81.35	42.37	67.55	71.80	39.01
pH 4.5 acetate buffer	10.78	2.79	11.98	8.98	1.60	14.97	53.37	81.35	52.17	56.24	86.18	47.87
pH 6.8 phosphate buffer	10.79	2.24	10.18	9.78	2.24	12.42	54.05	84.20	55.22	56.78	82.84	51.39

TABLE 12: STABILITY DATA FOR THE TRIAL FORMULATION OF ISOSORBIDE MONONITRATE SUSTAINED RELEASE TABLETS [TRIAL HT6]

Duration & Condition	Assay Results (In %) [95 to105%]	Mean Dissolution release in water (in %)							Difference (f1) and Similarity (f2) Factor		Related Substances (in %)	
		1st Hour	2nd Hour	4th Hour	6th Hour	8th Hour	10th Hour	12th Hour	f1 [<15]	f2 [>50]	Isosorbide 2- nitrate [NMT 0.5%]	Isosorbide dinitrate [NMT 0.5%]
Initial	100.3	29	39	58	76	87	95	99	2.82	80.29	Not Detected	Not Detected
40°C/ 75% RH												
1 Month	100.1	30	39	57	77	86	94	98	3.62	75.16	Not Detected	Not Detected
3 Months	99.5	31	38	58	79	87	94	99	3.82	76.32	Not Detected	Not Detected
6 Months	99.7	32	40	59	77	88	96	99	2.41	82.53	Not Detected	Not Detected
30°C/ 65% RH												
1 Month	100.2	28	37	57	74	86	95	99	4.23	74.11	Not Detected	Not Detected
3 Months	99.7	30	38	59	78	87	94	98	3.42	77.04	Not Detected	Not Detected
6 Months	99.9	29	40	60	78	88	95	99	2.01	84.57	Not Detected	Not Detected

TABLE 13: STABILITY DATA FOR THE TRIAL FORMULATION OF ISOSORBIDE MONONITRATE SUSTAINED RELEASE TABLETS [TRIAL CT6]

Duration & Condition	Assay Results (In %) [95 to105%]	Dissolution release in water (in %)							Difference (f1) and Similarity (f2) Factor		Related Substances (in %)	
		1st Hour	2nd Hour	4th Hour	6th Hour	8th Hour	10th Hour	12th Hour	f1 [<15]	f2 [>50]	Isosorbide 2- nitrate [NMT 0.5%]	Isosorbide dinitrate [NMT 0.5%]
Initial	100.1	28	37	57	75	84	94	98	4.83	71.02	Not Detected	Not Detected
40°C/ 75% RH												
1 Month	99.9	29	38	56	75	85	96	99	3.82	74.40	Not Detected	Not Detected
3 Months	99.9	30	38	58	77	86	95	98	3.42	76.67	Not Detected	Not Detected
6 Months	99.7	29	39	58	78	85	95	99	3.22	77.62	Not Detected	Not Detected
30°C/ 65% RH												
1 Month	99.9	29	36	56	73	85	96	99	4.63	70.91	Not Detected	Not Detected
3 Months	99.7	30	38	59	76	86	95	99	3.22	78.87	Not Detected	Not Detected
6 Months	99.8	28	36	56	74	83	93	97	6.04	66.51	Not Detected	Not Detected

TABLE 14: ANALYTICAL PARAMETERS FOLLOWED FOR STABILITY STUDY OF TRIAL FORMULATION HT6& CT6

Tests	Stationary Phase	Mobile Phase	Detection wavelength	Flow rate
Assay	C18; 250x 4.6 mm; 5µm [Inertsil ODS 3]	70:30 [Water: Methanol]	220 nm	1.0 mL/min
Dissolution	C18; 250x 4.6 mm; 5µm [Inertsil ODS 3]	52:48 [Water: Methanol]	220 nm	1.0 mL/min
Related Substances	C18; 250x 4.6 mm; 5µm [Inertsil ODS 3]	70:30 [Water: Methanol]	220 nm	1.0 mL/min

CONCLUSION: In the trial formulations using direct compression, the isosorbide mononitrate was directly compressed using DCCSRA and dicalcium phosphate (Emcompress). The process of direct compression was simple with two additives leading to saving of cost and time. The DCCSRA used in the formulation acted as retardant, binder and lubricant. No glidant was used to assist the flow of blend during compression. The calculated difference factor (f1 factor) and similarity factor (f2 factor) of trial batch HT6 and CT6 show that the dissolution release pattern of these batches were comparable to that of reference product [Imnit 60 tablet]. The above facts suggest that the DCCSRAs which have been prepared and evaluated in this study may be used as a multifunctional excipient in the sustained release formulation of Isosorbide tablets.

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