Research Article

Articulation Expansion including Artificial Insemination Estimation of Dextrometharphan Tablet by Solid Dispersion Recipe for Solubility Enhancement

Dr Zakir Hussain[1]*, Dr Mukkamalla Suresh[2], B.Hemalata[3], Shaik Shireen[3]

1. Professor and Head, Department of Pharmaceutics Vijaya College of Pharmacy. Munaganoor-Hyderabad, Telangana, India.
2. Professor, Department of Pharmaceutics, Vijaya College of Pharmacy, Munaganoor-Hyderabad, Telangana, India.
3. Assistant Professor, Department of Pharmaceutics, Vijaya College of Pharmacy, Munaganoor-Hyderabad, Telangana, India.

***Corresponding author's E-mail:** zakirhusains765@gmail.com

Received: 13-08-2022; **Revised:** 22-10-2022; **Accepted:** 30-10-2022; **Published on:** 15-11-2022.

ABSTRACT

The concept of formulating sustained release tablets using different polymers offers a suitable and practical approach of sustained in release and dissolution characteristics. Here the solubility of Dextromethorphan is enhanced by solid dispersions with PEG6000 as carrier. Then the formed solid dispersions are characterized and evaluated by drug content and *In vitro* dissolution studies. Among the various s solid dispersions prepared, the formulation SDF2 i.e., the solid dispersion of Dextromethorphan with PEG6000 prepared by Solvent Evaporation method shows faster dissolution rate it was decided to use formulations SDF2 to formulate sustained release tablets using different polymers like HPMC, EC and Guar gum by direct compression technique. Optimized formulation F4 which includes HPMC and EC has successfully sustained the drug release. The release process involves anomalous diffusion mechanism or diffusion coupled with erosion. FTIR studies show that there is compatibility between drug and excipients for the developed matrix tablets.

Keywords: Dextromethorphan, solid dispersions, drug content, direct compression technique, erosion.

QUICK RESPONSE CODE →

DOI: 10.47583/ijpsrr.2022.v77i01.010

DOI link: http://dx.doi.org/10.47583/ijpsrr.2022.v77i01.010

INTRODUCTION

The performance of these drug delivery systems is evaluated primarily in terms of their release kinetics and overall ease of administration. Methods that release drug with zero order kinetics (a time-dependent rate) for an extended time period are usually considered optimal.[3] Sustained release dosage forms furnish the following advantages over traditional dosage forms improvement of patient compliance and usage of less amount of drug, reduced local and systemic side effects, minimization of drug accumulation(with chronic dosage), reduction in potentiation or loss of drug activity (with chronic use), improvement in treatment efficiency, reduced fluctuating blood levels, increased bio-availability of some drugs, ability to provide special effects and reduction in cost of therapy.[4]

The most commonly used method for fabricating drugs in a controlled-release formulation is by incorporating them into a matrix containing a hydrophilic rate. In recent years, in association with progress and innovation in the field of pharmaceutical technology, there has been an increasing effort to develop prolonged release dosage forms form any drugs. Correspondingly, a growing number of new prolonged release dosage forms have been submitted for regulatory approval.[2] Prolonged release dosage forms have many advantages in safety and efficacy over immediate release drug products in that the frequency of dosing can be reduced, drug efficacy can be prolonged and the incidence and/or intensity of adverse effects can be decreased.[1] Oral solid dosage forms for sustained drug release has a major attention amongst all the controlled drug delivery systems due to conventional usage.

Drug Solubility

Solubility of active pharmaceutical ingredients (API) has always been a concern for formulators, since in adequate aqueous solubility may lead to development of parenteral products and limit use of oral products. Solubility plays an important role in drug disposition, since the maximum rate of passive drug transport across a biological membrane, is the product of permeability and solubility. Poor solubility has been identified as the cause of numerous drug development failures. For drugs that have very poor aqueous solubility, the rate at which the drug dissolves (dissolution) are often the slowest step and therefore exhibits a rate limiting effect on drug bioavailability. Therefore, one of the major current challenges of the pharmaceutical industry is related to strategies that improve the water solubility of drugs. Consequently, great efforts have been made to improve oral bioavailability of poorly water-soluble drug by increasing their dissolution rate through various techniques.[1]

Preparation techniques of solid dispersions[18,19]

A) Solvent evaporation method:

In this method, physical mixture of two components is dissolved in a common solvent and followed by the evaporation of solvent. The advantages of this method are low temperature requirement for the preparation of dispersion and thermal decomposition of drugs and carriers can be prevented. The higher cost of production, incomplete removal of solvent, adverse effects of solvent on the chemical stability of the drug and selection of common solvent are the draw backs of this method.

B) Melting method (Fusion method):[20,21]

The physical mixture of drug and water-soluble carrier was heated to melt and the molten mixture was then cooled and solidified mass was crushed, pulverized and sieved. The melting point of a binary system depends on its composition and proper manipulation of drug carrier ratios. Decomposition should be avoided due to fusion time and rate of cooling.

C. Kneading method:[22,23]

The physical mixture of drug and carrier were triturated using small quantity of organic solvent and water mixture, usually alcohol and water (1:1v/v). The slurry is kneaded for 45 minutes and dried at 45ºC. The dried mass is pulverized and sieved through sieve no 60 and the fraction was collected. The advantages of this method are low temperature requirement for solid dispersion preparation and usage of organic solvent is less. This method of preparation avoids thermal degradation of drug and employs less quantity of organic solvents.

D. Melting solvent method:[24]

This method involves dissolving the drug in a suitable solvent and incorporation of the solution directly into the molten carrier. This method possesses the advantages of both solvent and melting methods.

E. Supercritical fluid methods:

Supercritical fluid methods are mostly applied with carbon dioxide (CO_2), which is used as either a solvent for drug and matrix or as an anti-solvent. This technique consists of dissolving the drug and the carrier in a common solvent that is introduced into a particle formation vessel through a nozzle, simultaneously with CO_2. When the solution is sprayed, the solvent is rapidly extracted by the SCF, resulting in the precipitation of solid dispersion particles on the walls and bottom of the vessel. This technique does not require the use of organic solvent and since CO_2 is considered environmentally friendly, this technique is referred to as 'solvent free'. This technique is known as Rapid Expansion of Supercritical Solution (RESS).

MATERIALS AND METHODS

Materials

Dextromethorphan Polyethylene glycol 6000, HPMC K100, Ethyl cellulose, Guar gum, Micro crystalline cellulose, Magnesium stearate, Talc, Starch. All chemicals are of analytical grade API was purchased from Chandra labs Hyderabad and other excipients are procured as a gift sample.

Methodology[25]

Preparation of Standard Curve for Dextromethorphan

Determination of Standard Curve

Stock solution of 1000µg/ml of Dextromethorphan was prepared by dissolving 25 mg of drug in small quantity of methanol and diluted with pH 6.8 Phosphate buffer to 25ml. From this take 10 ml and make upto100 ml using buffer to get a stock solution of 100 µg/ml. From the above solution take 1,2,3,4 and 5ml dilute to 10 ml with buffer to get a concentrations of 10µg/ml, 20µg/ml, 30µg/ml, 40 µg/ml and 50 µg/ml. Explained in Figure-1 and 4. The absorbance of the different diluted solutions was measured in a UV spectrophotometer at 278nm. A calibration curve was plotted by taking concentration of the solution in µg/ml on X-axis and absorbance on Y-axis and correlation co-efficient "r^2" was calculated. Mentioned in Table-5.

Solid Dispersion of Dextromethorpan with polyethylene glycol-6000(PEG6000)

Methods of Preparation of Solid Dispersion:

Solid dispersions were prepared by different methods like physical mixture, solvent evaporation and fusion method.

Solvent evaporation method: [26]

Dextromethorphan and each of water- soluble carrier PEG 6000 were weighed accurately in various ratios (1:1, 1:2 and 1:3) and transferred to beaker containing sufficient quantity of acetone to dissolve. The solvent was evaporated at room temperature. The resulting solid dispersion was stored for 24 hrs in a desiccator to congeal. Finally, dispersion was passed through sieve no.85and stored in desiccators still further use.

Compatibility studies: The compatibility studies of dextromethorphan were studied by and results displayed in figure in 5 and 6.

Preparation of sustained release tablet of dextromethorphan solid dispersion by direct compression method

This sustained release tablets were prepared by direct compression method.

Sieving

The active ingredient was passed through the sieve#40 followed by the other ingredients were passed the same sieve.

Dry mixing

Dextromethorphan SD, Micro Crystalline Cellulose and different polymers and binder were taken in a poly bag and mixed for 5minutes to ensure uniform mixing of the ingredients with the drug.

Lubrication

Magnesium stearate and talc were weighed and they were passed through sieve #20. Then mixed with powdered blend of Dextromethorphan SD in a polybag for 5minutes to get a uniform blend. Mentioned in Table-1**.** Then the lubricated powdered blend of Dextromethorphan SD was weighed accurately and fed into the die of single punch machinery and compressed. For this 9mm round punch was used for compression.

Table 1: Composition of Dextromethorphan solid dispersions

Solid dispersion composition	Method	Drug-Polymer ratio	Formulation Code
Dextromethorphan: PEG 6000	Solvent evaporation method	1:1	SDPF1
		1:2	SDPF2
		1:3	SDPF3

Table 2: Composition of various sustained release formulations

Ingredients (mg)	F_1	F_2	F_3	F_4	F_5	F_6
Dextromethorphan SD	120	120	120	120	120	120
HPMC K100	10%	-	-	7.5%	-	12%
EC	-	10%	-	7.5%	7.5%	2.5%
Guar Gum	-	-	10%	-	7.5%	-
Starch	5%	5%	5%	5%	5%	5%
MCC	qs	qs	qs	qs	qs	qs
Magnesium Stearate	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%
Talc	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%
Total weight	300	300	300	300	300	300

Characterizations of dextromethorpan solid dispersion

Drug content[27]

An accurately weighed quantity of solid dispersion equivalent to 120 mg of Dextromethorphan was taken into a 100ml volumetric flask, dissolved in acetone and suitably diluted with 6.8 pH Phosphate buffer Mentioned in Table-7. The content of Dextromethorphan was determined spectrophotometrically at 278 nm against suitable blank using UV-visible spectrophotometer (1601, Shimadzu, Kyoto, Japan).

In vitro dissolution studies

The quantity of solid dispersion equivalent to 120 mg of Dextromethorphan was filled in colourless hard gelatine capsule by hand filling method. The dissolution study of capsules was conducted using dissolution testing USP apparatus 1 (basket method) in 900 ml of phosphate buffer of pH 6.8 at 37±0.5 ºC and at a speed of 50 rpm Mentioned in Table-2. Aliquot of 5ml was withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintain a constant volume after each sampling and analyzed spectrophotometrically at 278 nm against suitable blank using UV-visible spectrophotometer (1601, Shimadzu, Kyoto, Japan).

Evaluation parameters

Pre compression Parameters[28]

Flow Properties:

Angle of Repose:

- ✓ 20gms of the sample was taken
- ✓ The sample was passed through the funnel slowly to form a heap.
- ✓ The height of the powder heap formed was measured.
- ✓ The circumference formed was drawn with a pencil on the graph paper.
- ✓ The radius was measured and the angle of repose was determined. This was repeated three times for a sample.

Bulk density:

Bulk density is ratio of given mass of powder and its bulk volume. Bulk density was determined by measuring the volume of known mass of powder sample that has been passed through the screen in to graduated cylinder or through volume measuring apparatus in to cup.

$$\text{Bulk density} = M / V_0$$

Tapped density:

A known quantity of powder was transferred to a graduated cylinder and volume V_0 was noted. The cylinder fixed to a density determination apparatus, tapped for 500 times then reading was

observed. The density is achieved by mechanically tapped by a measuring cylinder containing the powder sample. After observing the initial volume, the cylinder is mechanically tapped and volume reading were taken until little further volume changes is observed. Listed in Table-3.

$$\text{Tap density} = M / Vr$$

Compressibility index and Hausner ratio:

$$\text{Compressibility index} = 100 \times \text{tapped density} / \text{bulk density}$$

$$\text{Hausner ratio} = \text{tapped density} / \text{bulk density}$$

Pre-Compression parameters

Table 3: Pre-Compression Parameters for Sustained release tablets

Code	B.D (gm/ml)	Blend Property				
		T.D (gm/ml)	C.I (%)	H.R	Angle of repose	Property
F1	0.721	0.87	17.126	1.206	27.28^0	fair
F2	0.461	0.608	24.177	1.32	24.21^0	passable
F3	0.41	0.483	15.113	1.178	26.16^0	fair
F4	0.710	0.873	19.714	1.251	29.32^0	fair
F5	0.453	0.583	22.299	1.288	22.43^0	passable
F6	0.500	0.600	23.22	1.295	23.46^0	Passable

Evaluation of tablets

The quantitative evaluation and assessment of a tablet's chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, disintegration and dissolution characters.

1. Physical Appearance:

The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, colour, presence or absence of odour, taste etc.

2. Size & Shape:

It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micro-meter or by other device. Tablet thickness should be controlled within a ± 5% variation of standard value.

3. Weight variation test:

Twenty tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. Not more than two tablets should differ in their average weight by more than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

4. Thickness and diameter:

The thickness and diameter of 10 tablets were recorded during the process of compression using vernier calipers.

5. Friability:

A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight mentioned in Table-4. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked.

Table 4: Post compression parameters for Sustained release tablets

Tablet Parameters	F1	F2	F3	F4	F5	F6
Average Weight (mg)	299	301	300	299	299	301
Hardness (Kg/cm^2)	6.8	6.4	6.7	6.5	6.4	6.7
Thickness (mm)	2.6	2.9	2.7	2.8	2.9	2.8
Friability (%)	0.25	0.70	0.55	0.62	0.75	0.28

The percentage friability was determined by the formula:

$$\% \text{ Friability} = (W_1 - W_2) / W_1 \times 100$$

Calibration curve of Dextromethorphan

Table 5: Standard calibration curve of Dextromethorphan in pH 6.8 Phosphate buffer

S.No	Concentration	Absorbance
1	0	0
2	10	0.116
3	20	0.212
4	30	0.311
5	40	0.411
6	50	0.522

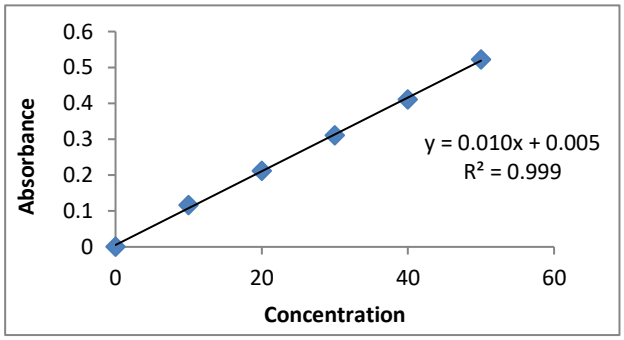

Figure 1: Calibration curve of Dextromethorphan at 278nm

In vitro Disintegration time

The U.S.P. device to test disintegration uses 6 glass tubes that are open at the top and 10 mesh screens at the bottom end. To test for disintegration time, one tablet is placed in each tube and the basket rack is positioned in a 1-L beaker of water, simulated gastric fluid or simulated intestinal fluid at 37 ± 2^0C such that the tablet remains 2.5 cm below the surface of liquid on their upward movement and not closer than 2.5 cm from the bottom of the beaker in their downward movement. Move the basket containing the tablets up and down through a distance of 5-6 cm at a frequency of 28 to 32 cycles per minute. Mentioned in Table-7. Floating of the tablets can be prevented by placing perforated plastic discs on each tablet. According to the test the tablet must disintegrate and all particles must pass through the 10 mesh screen in the time specified. If any residue remains, it must have a soft mass. If one or two tablets fail to disintegrate, the test is repeated using 12 tablets. Disintegration time: Uncoated tablet: 5-30 minutes.

Coated tablet: 1-2 hours

In vitro dissolution studies

The In vitro dissolution study was performed by using USP dissolution testing apparatus 2 (Paddle method). Weighed tablets from different batches were kept in a flask of the dissolution apparatus containing 900 ml of phosphate buffer of pH 6.8 dissolution medium maintained at 37±0.5ºC and at a speed of 50 rpm. Aliquot of dissolution medium (5ml) was withdrawn at specific time intervals and the samples were replaced with fresh dissolution medium Mentioned in Table-6. Aliquot were analyzed spectrophotometrically at 278 nm against Suitable blank using UV-visible spectrophotometer (1601, Shimadzu, Kyoto, Japan). Explained in Figure-2 and 3.

Table 6: *In vitro* drug release of various formulations

Time (hrs)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
0.5	7.2	3.1	4.5	3.1	5.1	4.8
1	21.8	26.5	19.2	18.3	17.4	8.7
2	40.6	32.4	38.6	30.8	20.7	15.7
3	69.1	41.8	50.8	41.6	28	19.8
4	83.8	56.8	73.4	58.7	37.6	23.8
5	90.8	70.9	81.8	64.3	43.8	31.7
6	95.6	86.8	90.3	76.8	51.4	36.8
7	--	99.2	98.6	89.2	63.4	43.2
8	--	---	--	95.8	75.4	59.6

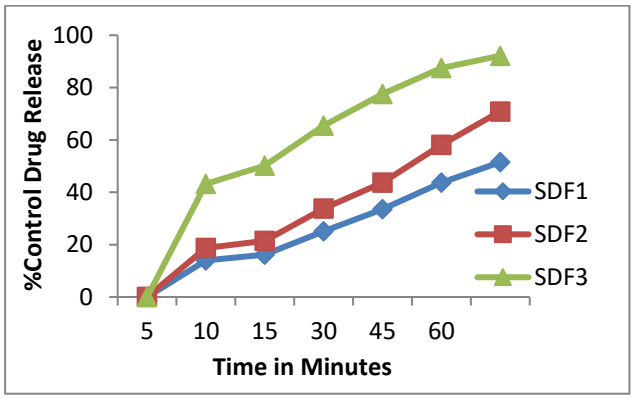

Figure 2: Cumulative Percent drug release for solid dispersion.

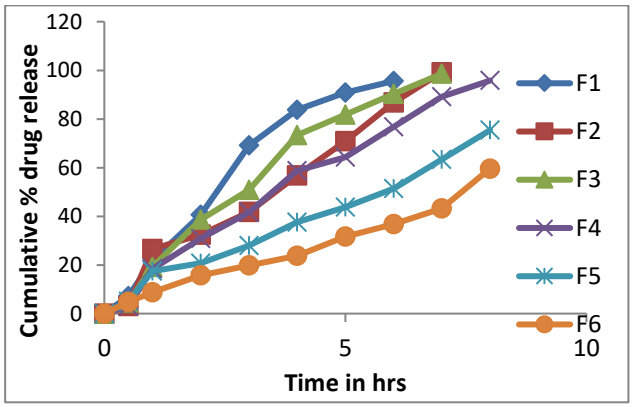

Figure 3: Cumulative Percent drug release for SR Tablet

Kinetic studies

Zero order equation

This equation describes the systems where the release rate is independent of the concentration of the dissolved species. The dissolution data are fitted into the zero order equation:

$$Q = Q_0 . K_0 t$$

Q = Amount of drug released at time t Q_0 = Amount of drug released initially K_0 = zero order rate constant

A graph of concentration vs. time would yield a straight with a slope equal to K_0 and the intercept at the origin of the axes. The zero order plot is derived from plotting the cumulative percent drug dissolved vs. time.

First order equation

The First order equation describes he release from systems where the dissolution rate is dependent upon the concentration of the dissolving species.

Release behavior generally follows the following first order release equation:

$$\ln M = \ln M_0 - K_1 t$$

M is the amount of drug undissolved at time t, M_0 is the amount of drug undissolved at t = 0 K_1 is the corresponding

release rate constant. A graph of log concentration of drug remaining vs. time a straight line with a negative slope

Peppas model fitting

The data obtained from *in vitro* release studies was fit into Peppas model. Koresmeyer-Peppas equation:

$$M_t/ M\infty = 1 – A (exp^{-Kt})$$

$$1og (1 - M_t/ M\infty) = 1og A – kt/2.303$$

M_t = Amount of drugs released at time t; $M\infty$ = Total amount of drug loaded; K = Diffusion constant/Release rate constant; R = regression co-efficient; n = time exponent

RESULTS

Drug Content:

Table 7: Drug Content

Parameter	SDPF1	SDPF2	SDPF3
Drug content (%)	75.71	90.1	87.5

The drug content in the solid dispersions was almost same and the assay was in the range and the assay did not drop in the solid dispersion the value was above 90%

UV Spectrum of Dextromethorphan

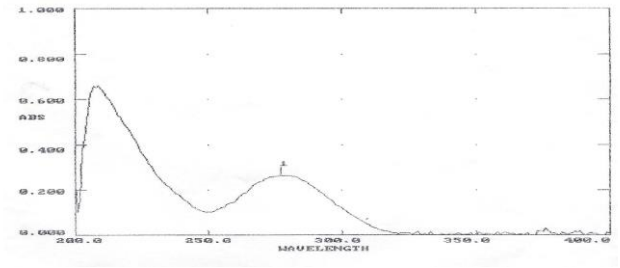

Figure 4: Spectrum of Dextromethorphan at 278nm by UV

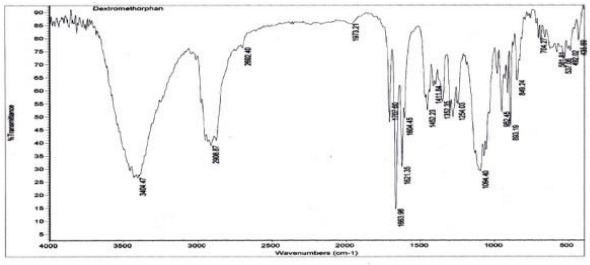

Figure-5 Drug and excipients compatibility studies

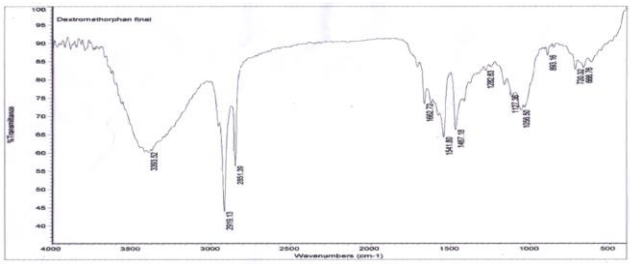

Figure-6 FTIR Spectra of Dextromethorphan Optimized formulation

Drug Release in solid dispersion

Table 8: Drug release in solid dispersion

Time (Mins)	SDPF1	SDPF2	SDPF3
5	39.3	42.12	43.2
10	50.12	57.19	50.12
15	63.02	69.7	65.4
30	70.29	81.8	77.6
45	75.71	90.1	87.5
60	80.15	98.15	92.17

Analysing the release profile, it was found SDF2 formulation with API and PEG 6000 with ratio 1:2 has shown maximum release compared with others.

CONCLUSION

The major problem in oral drug formulations is low and erratic bioavailability, which mainly results from poor aqueous solubility. Solid dispersions is the techniques are the most attractive processes to improve solubility of poorly soluble drugs. The concept of formulating sustained release tablets using different polymers offers a suitable and practical approach of sustained in release and dissolution characteristics. Here the solubility of Dextromethorphan is enhanced by solid dispersions with PEG 6000 as carrier. Then the formed solid dispersions is characterized and evaluated by drug content and Invitro dissolution studies. Among the various solid dispersions prepared, the formulation SDF2 i.e., the solid dispersion of Dextromethorphan with PEG 6000 prepared by Solvent Evaporation method shows faster dissolution rate it was decided to use formulations SDF2 to formulate sustained release tablets using different polymers like HPMC, EC and Guar gum by direct compression technique.

The prepared tablets of Dextromethorphan were evaluated for pre compression parameters like angle of repose, bulk density, tapped density, Carr's index and post compression parameters like the hardness, friability and weight variation, drug content and Invitro dissolution studies.

Among the various sustained release tablets of Dextromethorphan solid dispersion prepared, the formulation F4 shows complete release of drug in 8 hrs, which is considered as best formulation for sustained release tablets of Dextromethorphan.

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Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.