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Formulation and Evaluation of Sustained Release Pellets of Metformin Hydrochloride by Using Natural Polymer

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ABSTRACT

The purpose of present study was to formulation and evaluation of sustained release pellets of metformin hydrochloride by using natural polymer.*Blepharisrepens*is natural polymer extracted from *Blepharisrepens*leaves powder by using ethanol. Metformin hydrochloride capsule were formulated by using *Blepharisrepens*polymer and other excipients to sustain the drug release. Extracted polymer was evaluated for its flow properties. All the prepared capsules were evaluated for weight variation, disintegration time, drug content uniformity and in vitro drug release characteristics.*Blepharisrepens*polymer showed excellent flow properties and all values were within the limit. FTIR studies suggested that drug and polymers were compatible and did not show any chemical interaction. Weight variation and disintegration time were within the range of pharmacopoeia limit. The formulation F11 shows desired drug release anddrug content and i.e. 63.45% up to 12 h when compared with all other formulations. A lab scale method for extraction of *Blepharisrepens*polymer by ethanol precipitation method was developed. Through various evaluations, it was concluded that *Blepharisrepens*leaves polymer is an effective natural polymer and acts as a release rate modifier.

Keywords: *Blepharisrepens, In-vitro* drug release study, Metformin hydrochloride, Natural polymer, Sustained release capsule

INTRODUCTION

In recent years there have been important developments in different dosage form for existing and newly designed drugs, natural products and semi-synthetic as well as synthetic excipients often need to be used for variety of purpose. Gums and mucilage are widely used natural materials for conventional and novel dosage forms. These natural materials have advantages over synthetic ones since they are chemically inert, nontoxic, less expensive, biodegradable and easily available. They can also be modified in different ways to obtain tailor-made materials for drug delivery system and thus can compete with the available synthetic excipients. Various polymers have been investigated as a rate retarding agent, each presenting a different approach to the matrix system. The plant based polymer have been studied for their applications in different pharmaceutical dosage form like matrix controlled system, film coating agents, buccal films, microspheres, nanoparticles, various liquid formulations and their applicability and efficacy have been proven [1] .

The use of natural polymers and their semi-synthetic derivative in drug delivery continues to be an area of active research. Drug release retarding polymers are the key performer in matrix systems. Various polymers have been investigated as drug retarding agents, each presenting a different approach to the matrix system. Based on the features of the retarding polymer, matrix systems are usually classified into three main groups: hydrophilic, hydrophobic and plastic.Hydrophilic polymers are the most suitable for retarding drug release and there is growing interest in using these polymers in sustained drug delivery. There are various numbers of natural polymers which have been investigated as sustained release agent[2].

Blepharisrepens (Synonym: Acanthus repensVahl) which is a traditional medicinal herb of the family: Acanthaceae. Recently research has identified many valuable medicinal plants with potential for curing diseases and also as a source for preparing raw materials of pharmaceutical industry, like polymers. Preliminary phytochemical analysis of methanolic extract of whole plant powder reveledthe presences of alkaloids, tannins, carohydrates and saponins[4-5]. Based on features of retarding polymers, they are most suitable for retarding drug release and there is growing interest in using these polymers in sustained-release drug delivery.Present work covers isolation of natural polymer, its characterization & its utility as a natural retardant.

MATERIAL AND METHODS

Materials The plant of *Blepharisrepens*plants was collected from Aurangbad region in season of winter. The plant authentication was done from Botony department Dr. BAMU, Aurangabad. The active pharmaceutical ingredient (API) Metformin hydrochloride gift sample acquired from Harman Finochem Ltd.Sodium Carboxy Methylcellulose(SCMC), Magnesium Stearate, were obtained from TCI Chemicals, Mumbai. Acetone, ethanol and isopropyl alcohol (IPA) wereobtained from Rankem, India. Distilled water was used throughoutthe experiment.

Experimental Method

Isolation of polymer

- The collected plant were washed and cleaned then dried. Followed by size reduction using grinder.
- BR polymer was extracted by dissolving 500gm of *Blepharisrepens*leaves powder in 2000ml double distilled water and boiled with stirring up till the slurry was formed.
- Further, it was kept to cool for 3 to 4 hours so as to separate the supernatant liquid. The clear solution at the top was decanted and the rest was centrifuged at 10,000rpm for 5 minutes.
- This process was performed in each batch.
- The supernatant was separated and heated at 60ºC on water bath to concentrate the supernatant. The solution after heating was cooled to the room temperature and was then poured into twice the volume of acetone/ethanol with continuous stirring.
- The precipitates were formed and then the precipitated material was washed with distilled water and again dried at 50-60º under vacuum. The powder so obtained was stored in a desiccator until use.
- The extraction of *Blepharisrepens*leaves powder in ethanol and acetone were performed in 1:2 (Supernatant aq. part: organic solvent) ratio from these, the ethanol was gives better yield than acetone. On the basis of this result ethanol was taken for further study.

Fig No: 1. Refined *Blepharisrepens*polymer

Characterization of BR polymer[6]

Taxonomical classification. The collected *Blepharisrepens*leaves were classified for its kingdom, class, order, family, genus, and species.

Physical Evaluation: The polymer was evaluated for its colour, odour, appearance and taste as well as pH and swelling index.

Phytochemical Evaluation: The solution of 1% w/v extract was prepared using distilled water and evaluated for carbohydrates, alkaloid, glycosides, proteins, tannins, saponinsand flavonoids[6].

Flow Properties: Flow properties were evaluated by Angle of repose, Bulk density, Tapped density, Hausner's ratio, and Carr's index.

pH: pH of 1% w/v solution of *Blepharisrepens*leaves polymer was determined using pH meter.

Solubility Studies: Distilled water, hot water, Ethanol, 0.1N HCl, pH 6.8 Phosphate buffer solution were used to determine the solubility of Metformin hydrochloride.

Preparation of Metformin hydrochloride pellets for capsule formulation

The sustained release pellets of Metformin hydrochloridewas prepared by using wet Extrude speronization method. The formulations are composed of various concentrations of MagnesiumStearate, SCMC and polymer mixed with other excipients in various percentages. (Table no1) All powders were mixed. Drug was added to the mixture and mass was prepared using isopropyl alcohol:Water (7:3) and Propyl glycol. Then mass was passed o extrusion and speronization process and obtained pellets evaluated for several tests [7].

Experimental Design

The experimental design was developed with Design Expert software (Design Expert VR (Version 8.7.0.1 Stat- Ease, Minneapolis, MN) two level factorial design (23) was used. The formulation process variables and design matrix that consists of 8 experimental runs was constructed shown in table 1&2.

Table No: 1. Formulation and process variables &level

Sr. No.	Independent variables	Units	Levels	
			Low	High
1	Polymer concentration (%)	(%)	14.1	20.1
2	SCMC concentration (%)	(%)	8.4	14.4
3	Propyl glycol (%)	(%)	3.36	9.36

Table No2 Experimental design for Metformin hydrochloridepellets manufacturing

Batch	Drug (%)	SCMC (%)	BR (%)	Starch (%)	Magnesium Stearate (%)	IPA:Water (mL)	Propylene glycol (%)
Batch No. 1	57.3	11.4	17.1	3.1	4.4	7:3	6.36
Batch No.2	57.3	14.4	14.1	3.1	4.4	7:3	6.36
Batch No.3	57.3	14.4	17.1	3.1	4.4	7:3	9.36
Batch No.4	57.3	8.4	20.1	3.1	4.4	7:3	6.36
Batch No.5	57.3	11.4	20.1	3.1	4.4	7:3	9.36
Batch No.6	57.3	11.4	17.1	3.1	4.4	7:3	6.36
Batch No.7	57.3	8.4	17.1	3.1	4.4	7:3	9.36
Batch No.8	57.3	8.4	17.1	3.1	4.4	7:3	3.36
Batch No.9	57.3	11.4	17.1	3.1	4.4	7:3	6.36
Batch No.10	57.3	11.4	20.1	3.1	4.4	7:3	3.36
Batch No.11	57.3	14.4	20.1	3.1	4.4	7:3	6.36
Batch No.12	57.3	11.4	14.1	3.1	4.4	7:3	9.36
Batch No.13	57.3	8.4	14.1	3.1	4.4	7:3	6.36
Batch No.14	57.3	11.4	14.1	3.1	4.4	7:3	3.36
Batch No.15	57.3	14.4	17.1	3.1	4.4	7:3	3.36

Evaluation of pellets

Flow properties of pellets were evaluated by Angle of repose, Bulk density, Tapped density, Hausner's ratio, and Carr's index

Evaluation of Metformin hydrochloride capsule

Weight variation:
Five capsules were selected randomly and the average weight was determined. Then the individual capsules were weighed and the individual weight was compared with the average weight.

Disintegration test:
Introduce one capsule in each tube and suspend the apparatus in a beaker containing 60 ml of water at 37^0c. If hard capsules float on surface of water, the disc may be added. Operate the apparatus for 30 min, remove the assembly from the liquid and observed the residue remains on the screen of apparatus.

Drug content

Five capsules of each formulation were taken and remove the granules from capsules. The quantity of powder equivalent to 10 mg of drug was transferred into 100 ml volumetric flask and dissolve with distilled water by keeping in a sonicator for 10-15 min, then it was filtered, suitable dilutions were made and absorbance was recorded by using UV spectrophotometer at 234 nm.

***In- vitro* Drug Release**

Apparatus: Dissolution test apparatus -2; USP-32

Method: Paddle method
Dissolution medium: 0.1N HCl
Volume: 900 ml
Speed: 50 rpm

Procedure:

The capsule was placed inside the dissolution vessel. 5ml of sample were withdrawn at time intervals of 2h, 4h, 6h, 8h, 10h, 12h. The volume of dissolution fluid adjusted to 900 ml by replacing 5ml of dissolution medium after each sampling. The release studies were conducted with 6 capsules, & the mean values were plotted versus time Each sample was analysed at 234 nm using double beam UV and visible spectrophotometer against reagent blank.

Drug-excipient compatibility studies by FT-IR

IR spectroscopy is one of the analytical techniques useful in chemical reactions which is conducted using an IR Spectrophotometer. The spectrum was recorded in the wavelength region of 4000–400 cm−1. The IR spectra of pure drug (Paliperidone) and physical mixture of pure drug with polymer were determined by FT-IR using KBr dispersion method. The procedure consisted of dispersing a sample and compressing into discs by applying a pressure of 5 t for 5 min in a hydraulic press. The powder was placed in the light path and the spectrum was recorded.

RESULTS AND DISCUSSION

Characterization of polymer

Taxonomical classification

Based on Taxonomical classification *Blepharisrepens*is classified under the Kingdom of Plantae, Order of lamiales, and family as Acanthaceae. The detail classification is shown in Table 3.

Table3:Taxonomical classification of*Blepharisrepens*

Taxonomical hierarchy	
Kingdom	Plantae
Common Name	Hadsan
Order	lamiales
Family	Acanthaceae
Genus	Blepharis
Species	repens

Physical characterization of *Blepharisrepenspolymer*

The extracted polymer powder appeared in slightly yellowish to brownish colour with no characteristic odour. The polymer is solublein hot water producing viscous solution. Polymer also shows swelling index and pH 5.64. *Blepharisrepens*leaves produced 7.2% of dried polymer in ethanol,All the valuesare depicted in Table 4.

Table4:Physical characterization of *Blepharisrepenspolymer*

Physical Properties	Observation
Appearance	Powder
Colour	Slightly yellowish to brown
Odour	No odour
Taste	Tasteless
Solubility	In hot water
Swelling index	3
pH	5.64
% yield	7.2%

Phytochemical characterization of *Blepharisrepenspolymer*

Phytochemical test for carbohydrates, alkaloid, glycosides, proteins, tannins, saponins and flavonoids were carried out using respective reagents. Results revealed that there was presence of alkaloid, tannins, carbohydrates, proteins, glycosides, saponins and flavonoids in ***Blepharisrepens***polymer shown in table 5.

Table 5: Phytochemical characterization of *Blepharisrepenspolymer*

Phytochemical test	Result obtained
Carbohydrates	+ve
Proteins	+ve
Alkaloids	+ve
Glycosides	+ve
Tannins	-ve
Flavonoids	+ve
Saponins	+ve

Flow properties of *Blepharisrepenspolymer*

Dried ***Blepharisrepens***leaves polymerhas an excellent flow property based on Angle of repose 23 ± 0.7 Bulk density 0.7360 ± 0.8 g/cm3, and Tapped density 0.7945 ± 0.3 g/cm3. Based on USP, Carr's index with value of 7.00±0.1 % and Hausner's ratio of 1.120 ± 0.8 noted values in excellent range of flowability. The polymeris now confirmed very suitable to be used in pellets preparation. All these values are tabulated in Table 6.

Table 6:Flow properties of *Blepharisrepenspolymer*

Flow properties	Observation
Angle of repose	23 ± 0.7
Bulk density	0.7360 ± 0.8 g/cm3
Tapped density	0.7945 ± 0.3 g/cm3
Carr's index	7.00±0.1 %
Hausner's ratio	1.120 ± 0.8

Drug-excipient compatibility studies by FT-IR

Drug- excipient interactions play an essential role to release of drug from the formulation. The IR spectrum of polymer and physical mixture of drug and polymer were studied. The characteristic absorption peaks of Metformin hydrochloride were obtained. From the spectra of pure drug Metformin hydrochloride and the combination of drug with polymers, it was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, thus indicating compatibility of the drug and polymer. IR spectra of the polymere drug in combination with the polymers are shown in Figure No.2 and 3.

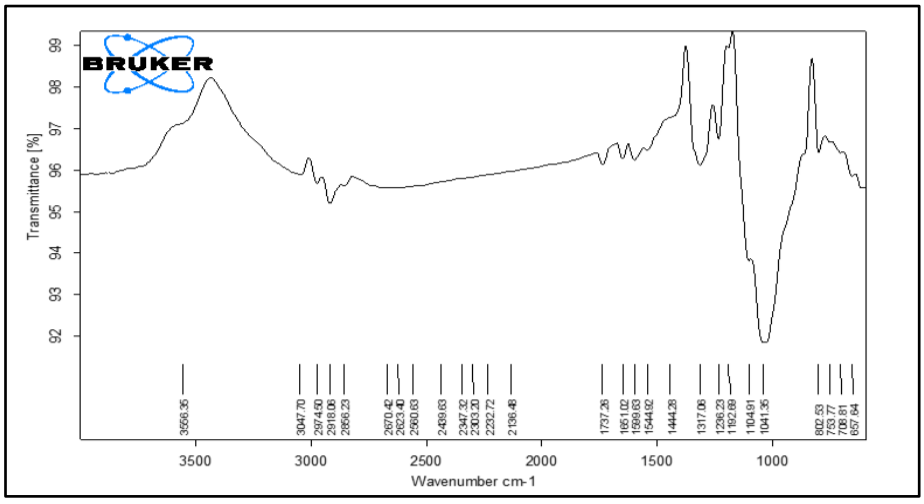

Fig. 2: FTIR spectra of polymer

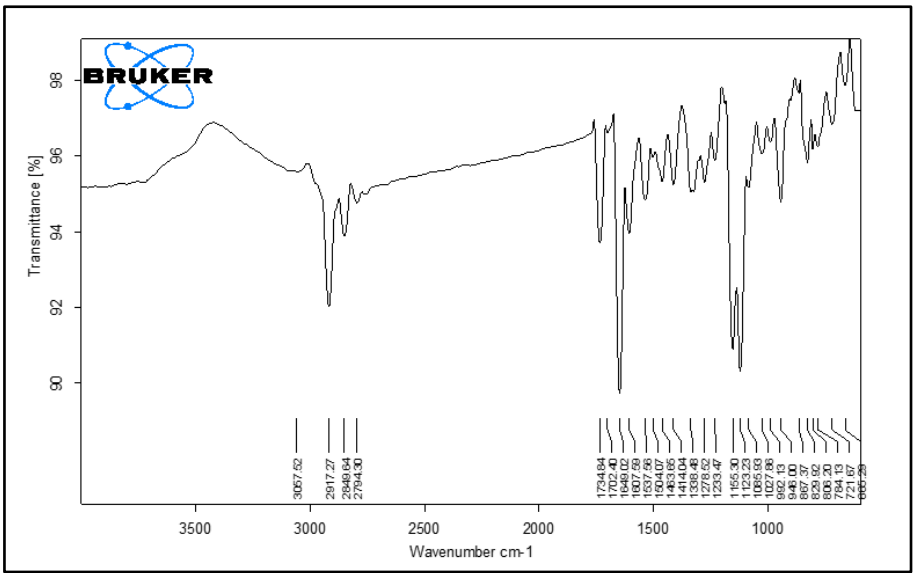

Fig. 3: FTIR spectra of physical mixture of Metformin hydrochloridewith polymer

Standard curve of Metformin hydrochloride

The standard curveof Metformin hydrochloridewas obtained by using the different concentration of Metformin hydrochloride i.e. 1, 2, 3, 4, 6, and 8µg/ml with the selected wavelength (234nm) show in table 7.The graphicalpresentation was determined by plotting absorbance againstconcentration (µg/ml) and obtained a fine linear regression line withR value of 0.9977 as shown in Fig. 4. This standard linewas adopted as a standard reference graph which was later used to calculatethe concentration of drug released with correspondedabsorbance value at particular instance during vitro dissolutionstudies.

Table 7:UV analysis of Metformin hydrochloride

Sr. No.	Concentration(µg/ml)	Absorbance
1	1	0.0962
2	2	0.1934
3	3	0.2984
4	4	0.4218
5	6	0.5988
6	8	0.7824

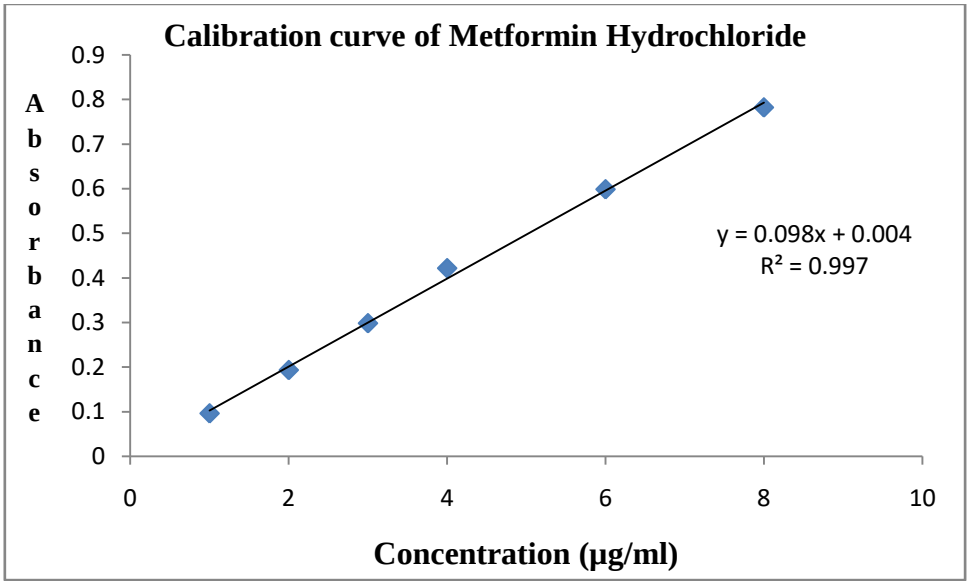

Fig No: 4. Calibration curve of Metformin hydrochloride

Evaluation ofMetformin hydrochloride pellets

Flow properties ofpellets was evaluated by determining Angle of repose, Bulk density, Tapped density, Hausner's ratio, and Carr's index with an acceptable limit.Table No.8 depicted the result of evaluation parameters of pellets of all formulation. The bulk density & tapped density for all formulation varied in the range of 0.7306 to 0.8202 and 0.7200to 0.8219respectively. The Carr's index for all formulation was found to be in the range of 2.00 to 14.0. Hausner's ratio for all powder granules was found to be in the range 1.15 to 1.24, also the angle of repose for powder granules of all formulation range between 1.02 and 1.09thus, it showed that all formulations showed good compressibility and good flow properties.

Table 8: Flow properties of pellets

BatchCode	Bulk Density* g/mL	TabDensity* g/cm	Angle of repose* (θ)	Carr's Index* (%)	Hausner's ratio*
Batch No.1	0.7702 ± 0.2	0.7200 ± 0.2	18 ± 0.2	6.00±0.3	1.063 ±0.1
Batch No.2	0.7563 ± 0.3	0.7406 ± 0.2	22 ± 0.1	2.00±0.2	1.022 ± 0.3
Batch No.3	0.7780 ± 0.2	0.7785 ± 0.5	21 ± 0.6	16.0±0.1	1.086 ± 0.4
Batch No.4	0.7408 ± 0.1	0.7360 ± 0.8	19 ± 0.7	8.00±0.1	1.041 ± 0.6
Batch No.5	0.7747 ± 0.1	0.7408 ± 0.8	18 ± 0.1	4.00±0.2	1.086 ± 0.1
Batch No.6	0.7473 ± 0.6	0.7453 ± 0.2	24 ± 0.4	6.00±0.4	1.063 ± 0.4
Batch No.7	0.8202 ± 0.5	0.7358 ± 0.5	25 ± 0.3	10.0±0.7	1.063 ± 0.7
Batch No.8	0.7306 ± 0.2	0.7395 ± 0.7	22 ± 0.2	10.0±0.3	1.020 ± 0.3
Batch No.9	0.7406 ± 0.2	0.8219 ± 0.3	19 ± 0.5	6.00±0.3	1.190 ± 0.4
Batch No.10	0.7785 ± 0.5	0.7852 ± 0.4	22 ± 0.6	14.0±0.2	1.099 ± 0.3
Batch No.11	0.7360 ± 0.8	0.7945 ± 0.3	23 ± 0.7	7.00±0.1	1.120 ± 0.8
Batch No.12	0.7408 ± 0.8	0.7625 ± 0.4	18 ± 0.2	8.00±0.1	1.092 ± 0.6
Batch No.13	0.7453 ± 0.2	0.7511 ± 0.7	25 ± 0.1	4.00±0.3	1.073 ± 0.7
Batch No.14	0.7358 ± 0.5	0.7344 ± 0.3	24 ± 0.3	4.00±0.2	1.088 ± 0.9
Batch No.15	0.7395 ± 0.7	0.7499 ± 0.7	18 ± 0.8	6.00±0.2	1.087 ± 0.2

Evaluation of Metformin hydrochloride Capsule

The Metformin hydrochloride sustained release capsule was produced using extrude speronizationmethod. The capsules were evaluated for its physical parameters such as %Drug release,Friability of pellets, drug content, (Table no. 8)

%Drug release:

The percentage drug release of all the formulations were found to be between 63.45% to 95.46% which was within the acceptable limits as per IP.

Friability of pellets

Friability of pellets formulation was found in the range of 0 – 0.7 %. Upper permissible limit for friability is 0.8 % and it was found that all batches pass the test for friability

Drug Content

The percentage drug content of all the formulations were found to be between 78.21% to 93.75%which was within theacceptable limits as per IP shown in table 9.

Table 9: Evaluation parameter of Capsule

Batch Code	%Friability of pellets	%Drug release	% Drug content
Batch No.1	0.1	75.53	87.22
Batch No.2	0.4	93.56	78.21
Batch No.3	0.3	79.48	92.23
Batch No.4	0	65.42	92.52

Batch No.5	0.5	66.52	87.46
Batch No.6	0.4	76.38	87.98
Batch No.7	0.2	71.52	87.19
Batch No.8	0.3	70.61	87.35
Batch No.9	0.5	72.46	87.42
Batch No.10	0.7	64.25	92.65
Batch No.11	0.4	63.45	93.75
Batch No.12	0.6	95.26	79.68
Batch No.13	0.5	92.75	78.45
Batch No.14	0.7	91.63	85.26
Batch No.15	0.2	73.96	80.24

***In- vitro* Drug Release**

In present study of dissolution profile as shown in Fig. 5,6,and7 all the formulations have shown more than 60% of drugs being released within 12 h in 0.1 N HCL. From the observation Batch 1, 4, 10 and 11 has achieved drug release 75.53, 65.42, 64.25, 63.35 respectively within 12 h. whereas Batch 11 was able to achieve 63.35% drug release. This comparison can be concluded that formulation Batch 11contain maximum amount of polymer i.e.20.1%(Fig.11)which able to sustain the maximum drug release shown in table 13. The *in-vitro* drug release was tabulated in Table10, 11 and 12.

Table No: 10. % Drug release of batch1- batch 5

Time (hrs.)	Batch-1	Batch-2	Batch-3	Batch-4	Batch-5
0	0	0	0	0	0
2	13.99	22.18	23.27	8.99	9.21
4	23.84	38.25	28.24	18.84	19.77
6	38.22	49.21	44.26	32.22	36.52
8	51.86	68.15	56.42	48.86	50.72
10	68.48	89.54	75.37	57.48	59.45
12	75.53	93.56	79.48	65.42	66.52

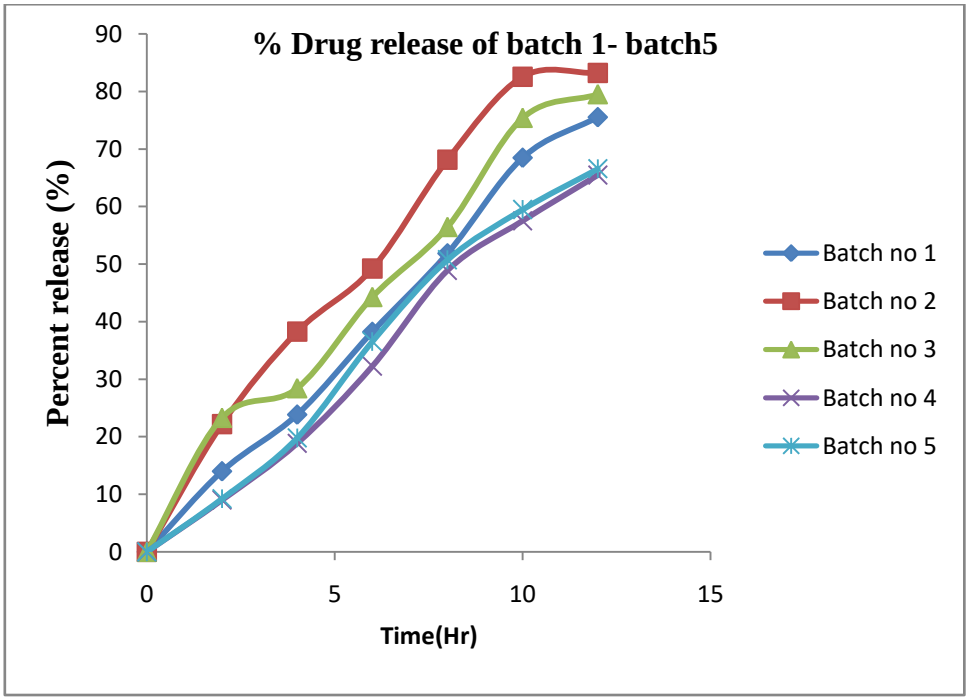

Fig No: 5. Dissolution profile of batch batch 1- batch5

Table No: 11. % Drug release of batch 6- batch 10

Time (hrs.)	Batch-6	Batch-7	Batch-8	Batch-9	Batch-10
0	0	0	0	0	0
2	14.21	11.27	10.42	12.42	8.74
4	24.18	22.93	21.63	24.35	18.22
6	40.27	39.45	37.81	39.45	31.42
8	53.86	49.85	45.21	48.85	45.75
10	69.49	63.89	62.86	66.74	56.52
12	76.38	71.52	70.61	72.46	64.25

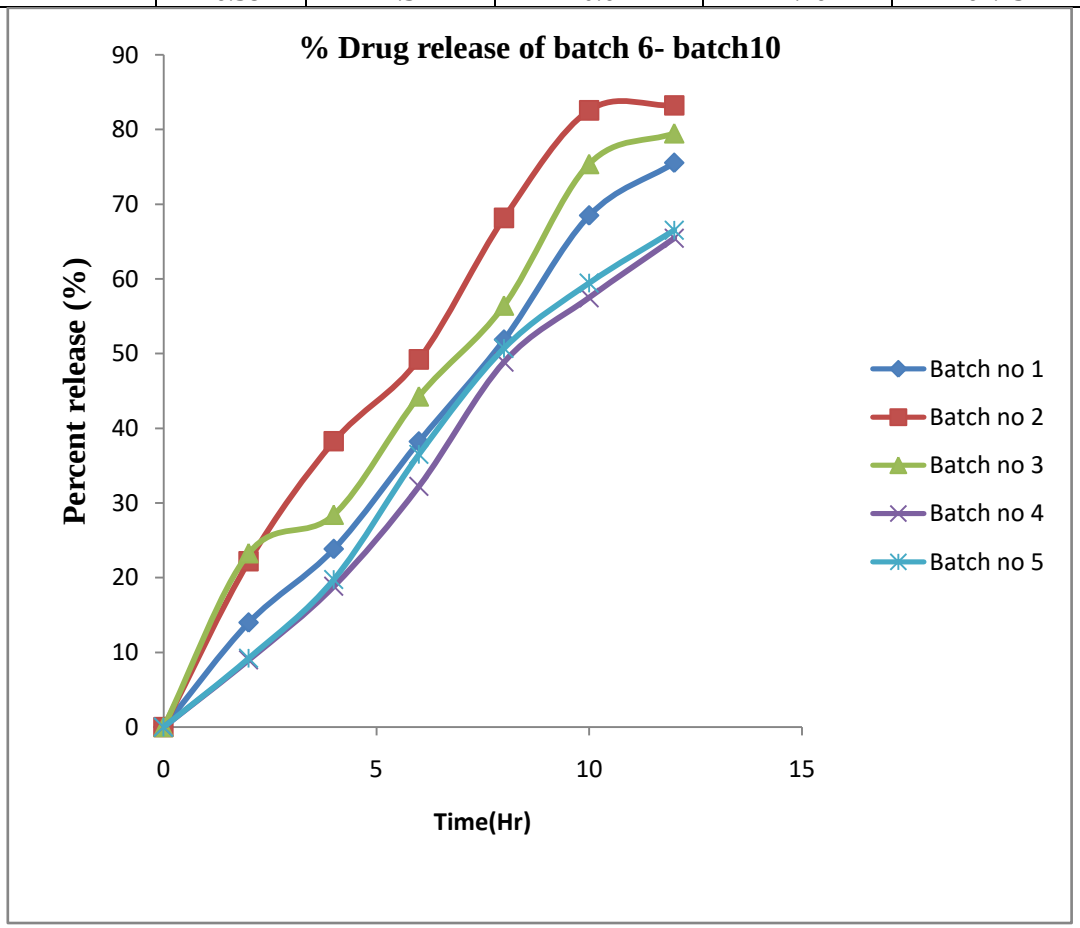

Fig No: 6. Dissolution profile of batch batch 6- batch10

Table No: 12. % Drug release of batch 11- batch15

Time (hrs.)	Batch-11	Batch-12	Batch-13	Batch-14	Batch-15
0	0	0	0	0	0
2	8.62	21.24	22.14	20.65	12.47
4	19.11	38.34	37.57	37.89	24.78
6	30.24	50.14	50.24	48.99	40.57
8	45.45	67.98	66.68	68.42	48.24
10	57.11	89.12	88.45	87.98	65.24
12	63.45	95.26	92.75	91.63	73.96

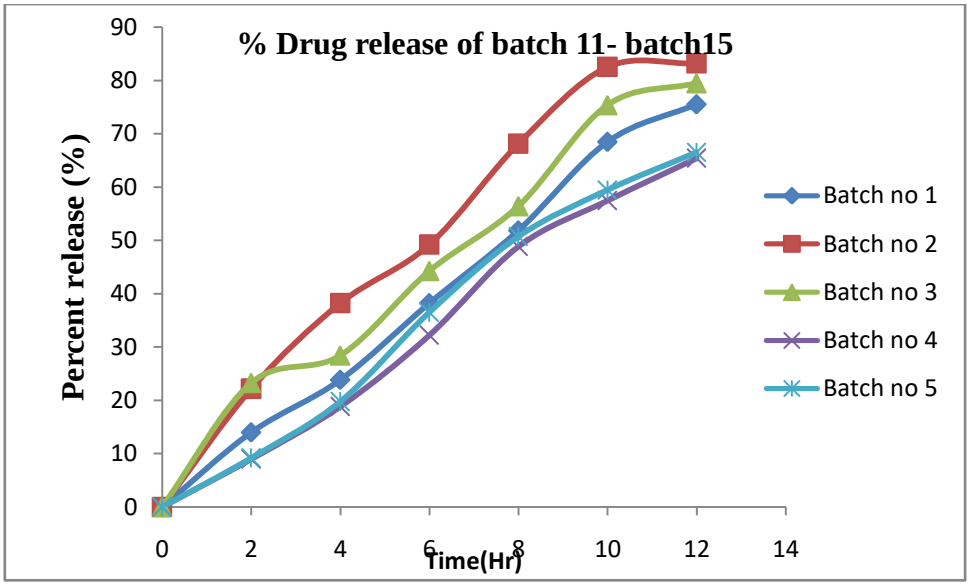

Fig No: 7. Dissolution profile of batch 11- batch15

RSM graphs for percent drug release of Metformine Hydrochloride

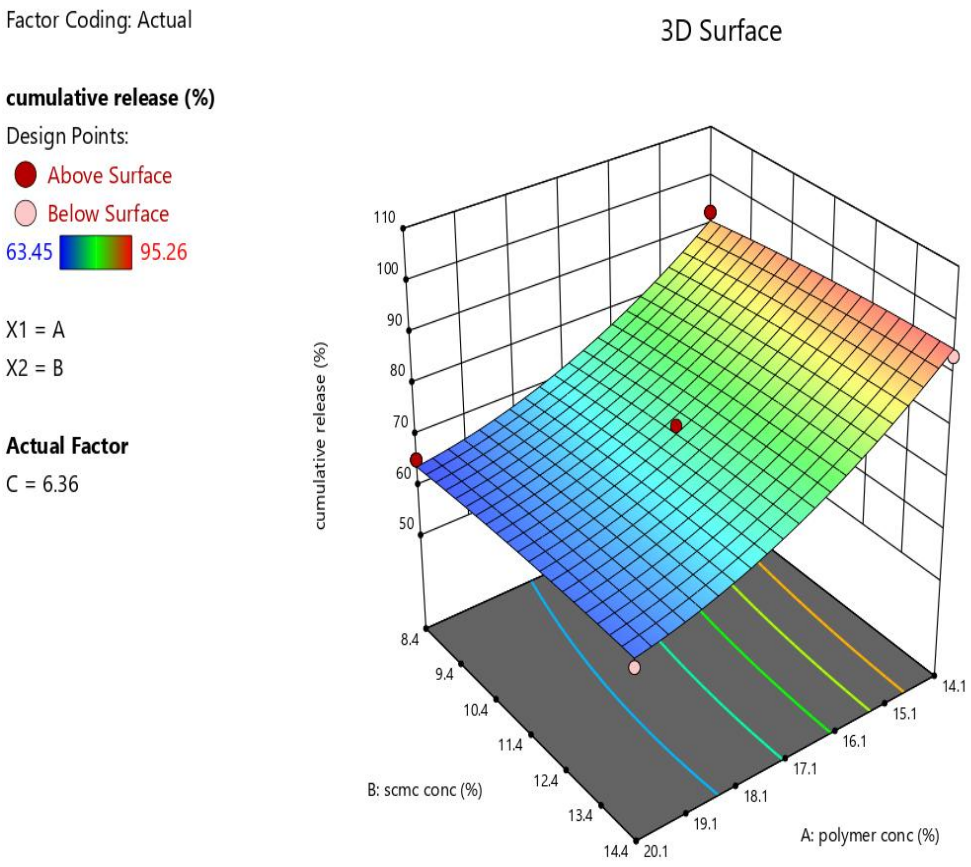

Fig No:8. Effect of BR Polymer and SCMC concentration on drug release

This response plot shows the effect of SCMC and BR Polymer concentration on drug release.When the polymer concentration in the formulation increased, drug releasedecreased. SCMC is used as support polymer in formulation; it shows no effect on release of drug.

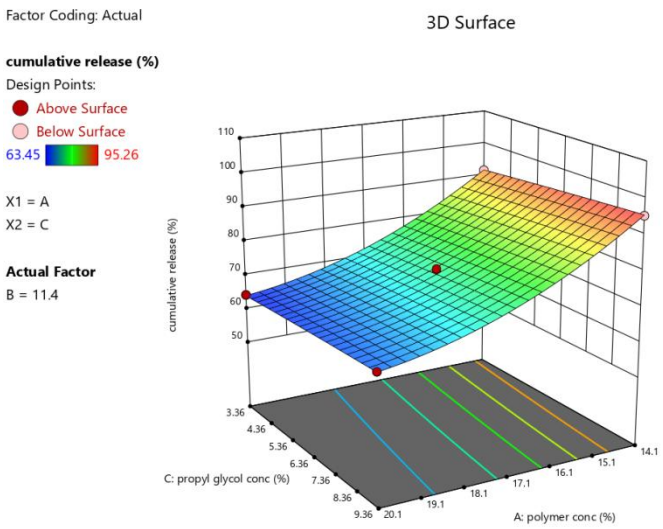

Fig No: 9. Effect of BR Polymer and Propyl glycol concentration on drug release

This response plot shows the effect of BR Polymer and Propyl glycol concentration on drug release. The polymer is used in the sustained release due to its viscosity which plays a major role in the sustained release behavior of the pellets.In RSM plot when the polymer concentration is high, the release the drug will be low.There is slightly increase in release on increasing conc of propyl glycol but it is used as binder. Hence we have to use optimized propyl glycol concentration.

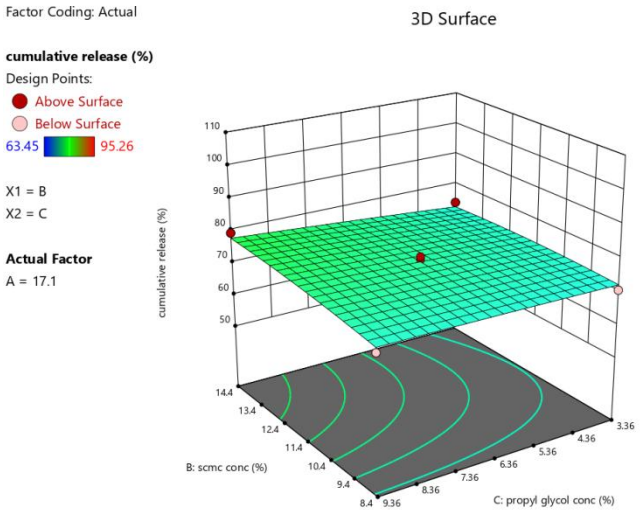

Fig No: 10. Effect of SCMC and Propyl glycol concentration on drug release

This response plot shows the effect of SCMC concentration and Propyl glycolconcentration on drug release. The double effect of the binder and wetting agent on the release profile was observed. If we increase SCMC and Propyl glycol concentration it leads to slightly increase in drug release.

Table 13.Dissolution profile of optimized batch (Batch-11)

Batch no.11-OB		
Time (hrs.)	**Time (hrs.)**	**Time (hrs.)**
0	0	0
2	2	2
4	4	4
6	6	6

8	8	8
10	10	10
12	12	12

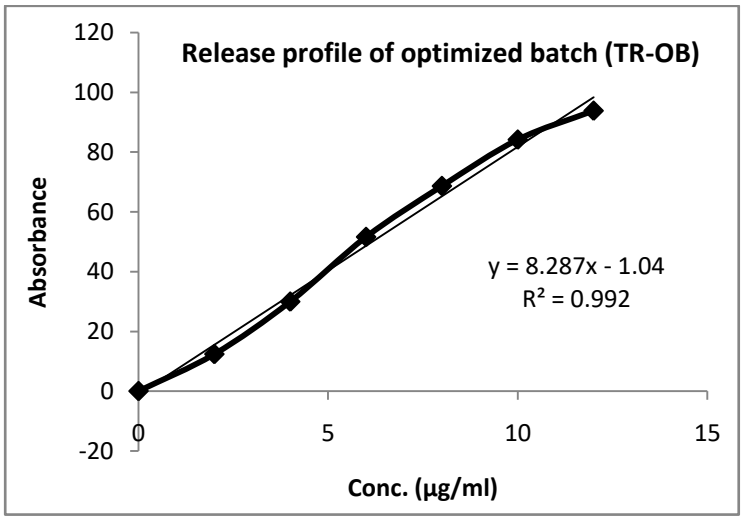

Fig No: 11. Dissolution profile of batch Batch-OB

CONCLUSION

A lab scale method for extraction of *Blepharisrepens* polymer by ethanol precipitation method was developed. The potential of *Blepharisrepens* polymer as a release rate modifier was established using Metformin Hydrochloride as a model drug. Development of Metformin Hydrochloride formulation by DE (Design Expert) showed that *Blepharisrepens*based polymer has a potential to act as release rate modifier.

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