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Development of sustained release polyherbal formulation of *Alstonia scholaris, Centella asiatica, Corchorus trilocularis* and *Morinda pubescens* for anti-diabetic activity

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Abstract
Diabetes mellitus is a chronic metabolic disorder caused by insufficient production of insulin. In type 1 diabetes mellitus there is failure in production of insulin as a result of destruction of the β cell of pancreas and in type 2 diabetes mellitus can be characterized by defect in both insulin action and insulin secretion and it is associated with elevated basal glucose production. The main aim of the present work was to formulate and evaluate Polyherbal antidiabetic sustain release matrix tablets of leaves of *Alstonia scholaris*, *Centella asiatica*, *Corchorus trilocularis*, *Morinda pubescens*.

Keywords: herbal drugs, sustained release, antidiabetic agent, polyherbal tablets

Introduction
Sustained release system is types of modified drug delivery system that can be used as a replacement to conventional dosage system. Sustained release system has various benefits like patient compliance, avoid multiple dosing, cost effectiveness, flexibility, increase the plasma drug concentration, avoid side effects and overcome the problems associated with conventional drug delivery system. [1, 2]
Alstonia scholaris is the tree of family Apocyanaceae, has a promising place in the Ayurvedic system of medicine due to its various medicinal values like antidiabetic, antibacterial, antianxiety, anticancer, hepatoprotective, anti-inflammatory, analgesic effects. The leaves have been used traditionally as folk remedies for the treatment of many diseases including diarrhea, dysentery, and malaria and snake bites. The plant is rich in alkaloids, flavonoids, saponins, steroids, reducing sugars and phenolic compounds which witness the ample amount of medicinal potential of the herb [3].*Centella asiatica*, a perennial herbaceous creeper belongs to the family Umbellifere (Apiceae). It is widely used as a blood purifier as well as for treating high blood pressure, for memory enhancement and promoting longevity. The other reported activities are anti-inflammatory, anticancer, antiulcer, anxiolytic, anticonvulsant, antidepressant, antioxidant, immuno modulating, cardioprotective, hepatoprotective, radio protective activity, wound healing, memory enhancing activity, burns, anti-psoriatic activity, antimicrobial activity, anti-hyperglycemic and neuroprotective activity[4-14].*Corchorus trilocularis* L. (Tiliaceae) is one of the most commonly plants in India. The edible leaves of *Corchorus* species are reported to contain some trace mineralsuseful to alleviatemineral deficiencies of the human body. The seed sare hot with a sharp taste, alexipharmic, removes tumors, pain, stomach troubles, skin diseases, and scabies. The leaves are reported to prevent cardiovascular disorders and in treatment of diabetes mellitus [15].*Morinda Pubescens* is a flowering shrub-like species belonging to family Rubiaceae. *M. pubescens* is listed as traditional Indian herbal antidiabetics [16]. Traditionally, all parts of the plant especially the leaves and root, are widely used by indigenous people for medicating a full spectrum of ailments and diseases ranging from the topical application to heal wounds, inflammation, gout and stomach pains to oral administration for diabetes, malaria, fever, rheumatism and infectious diseases[17].The antidiabetic activity of the polyherbal extract of the leaves of *Alstonia scholaris*, *Centella asiatica*, *Corchorus trilocularis*, *Morinda pubescens* is already reported [18].

Materials and methods
Collection and Authentication of Plant Material:
The dried leaves of *Alstonia scholaris*, *Centella asiatica*, *Corchorus trilocularis* and *Morinda pubescens* were purchased from authorized local herbal supplier at Indore (M.P.). The dried leaves of above mentioned were identified and authenticated by the Dr. S. N. Dwivedi, Prof. and Head, Department of Botany, Janta PG College, APS University, Rewa, M.P. and herbarium specimen was submitted in Department of Botany for future references. The Voucher No. J/Bot/ASL,078 CAL079, CTL080 & MPL081.

Preparation of Extracts
The leaves of *Alstonia scholaris*, *Centella asiatica*, *Corchorus trilocularis* and *Morinda pubescens* were air dried and separately coarsely powdered in a grinder. 500 g of each crude drug powder were extracted with ethanol and distilled water (Hydro-alcoholic solvent) in the ratio of 70:30 using soxhlet apparatus [19-22].The extracts were concentrated under vacuum, dried at about 60 ˚C and then stored in a refrigerator for further use. The polyherbal extract was prepared by mixing *Alstonia scholaris*, *Centella asiatica*, *Corchorus trilocularis* and *Morinda pubescens* extract in the ratio 1:1:1:1.

Development of Poly herbal Matrix tablets

Poly Herbal extract, Dicalcium phosphate anhydrous, hydroxypropylmethyl cellulose (HPMC K100 LV), (HPMC K4M) and maltodextrin were sifted through # 20 mesh sieve. The whole blend was resifted through # 20 mesh sieve. The above blend was mixed in blender for 10 minutes followed by blending with magnesium stearate (presifted through # 40 mesh sieve) for 2 minutes. The lubricated blend was compressed on 20 station rotary tablet compression machine using 16 mm flat punches to get slugs at the hardness of 70 -80 N and machine speed of 20 -25 rpm. The slugs obtained were milled using multimill with 8 mm screen followed by 1.5 mm screen with knife forward and slow speed. The sized granules were sifted through # 20 mesh sieve. The above sized granules were lubricated again in the container blender with magnesium stearate (presifted through # 40 mesh sieve) for 2 minutes. The final blend was compressed on 20 station rotary tablet compression machine using 8.00 mm ("B" tooling) biconvex punches plain on both sides at hardness of 50 -70 N and machine speed of 20 -25 rpm. Images of formulated tablets is given in Figure No.1 and table no.1 [23]

Table 1: Composition of formulation with Hydroxypropylmethyl cellulose as retarding polymer (B. size: Each batch of 100 tablets)

Ingredients	HPMC-1	HPMC-2	HPMC-3	HPMC-4	HPMC-5	HPMC-6	HPMC-7	HPMC-8	HPMC-9	HPMC-10
Poly Herbal Extract	30	30	30	30	30	30	30	30	30	30
Dicalcium phosphate anhydrous	59	52	57	52	46	48	50	48	55	40
Maltodextrin	70	64	57	57	57	57	57	57	58	58
(HPMC K100 LV)	34	44	44	44	50	48	46	46	35	35
(HPMC K 4 M)	5	10	10	15	15	15	15	17	20	35
Magnesium stearate	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Average wt. (mg)	200	200	200	200	200	200	200	200	200	200

Evaluation Parameters

The formulated tablets were assessed for its general appearance, Weight variation test, Thickness, Hardness test and Friability test [24-26] and observations were made for shape, colour, texture and odour. Drug content [27] & *In vitro* Dissolution Study were also determined. [28]

Results and discussion

Sustained release tablets were prepared by dry granulation method as per formulae are given in Table1.

Fig 1: Prepared Sustained Release Poly Herbal Tablets with Hydroxy propylmethyl Cellulose

Table 2: Evaluation parameters of formulated polyherbal tablet

Weight Variation (n=20)mg	200.11±0.13	200.05±0.11	199.9 ±0.27	199.2±0.28	200.02±0.09	200.01±0.19	200.16±0.09	199.99±0.12	200.19±0.11	200.04±0.19
Thicknessmm(n=3)	3.4±0.19	3.7 ±0.13	3.24±0.17	3.1±0134	3.4 ±0.20	3.4 ±0.27	3.4±0.16	3.4±0.16	3.4±0.12	3.4±0.15
Hardness Kg/cm^2 (n=3)	5.61 ±0.283	5.20±218	5.31±0.113	5.42±0.218	5.35±0.111	5.67±0.213	5.76±0.232	5.42±0.123	5.36±0.213	5.37±0.203
Friability%	0.57	0.56	0.51	0.59	0.56	0.57	0.55	0.58	0.58	0.57
Drug Content %(n=3)	94.02±0.70	99.27±0.16	95.52±0.27	99.37±0.62	97.24±0.17	97.63±0.18	97.86±0.36	99.26±0.12	95.35±0.12	99.12±0.11

The tablets thickness was also used to assess the quality of the tablet under uniform conditions of manufacturing process. Thickness of the tablets ranged from 3.1- 3.7 mm. The total weight of each formulation was not maintained uniformly however the weight variation of the tablets within the limits of ± 1%. Friability values were found to be less than 1% in all prepared formulations and considered to be satisfactory. Drug content of HPMC was found 99.12%.

Table 3: Comparative % dissolution profile of polyherbal SR tablets containing Hydroxypropyl methyl cellulose as polymer with Diamicron SR tablets

Time in Hrs	Cumulative drug release										
	Diamicron SRtablets	HPMC-1	HPMC -2	HPMC-3	HPMC-4	HPMC-5	HPMC-6	HPMC-7	HPMC-8	HPMC-9	HPMC-10
1	7	9.45	16.4	10.4	9.9	12.6	12.7	11.1	3.2	4.8	10.5
2	15.8	17.9	21.4	17.5	10.2	14.7	15.9	16.8	12.8	14.9	15.9
4	36.6	31.4	45.1	36.4	23.4	33.7	39.8	37.2	25.8	28.8	39.6
6	54.2	61.7	60.4	56.6	34.4	44.5	58.2	54.1	44.9	48.9	56.6
8	80.9	75.4	66.7	74.3	52.7	49.7	61.6	79.4	58.7	62.3	81.7
10	97.2	82.5	76.5	78.1	60.1	64.2	78.9	84.6	63.5	81.5	95.1

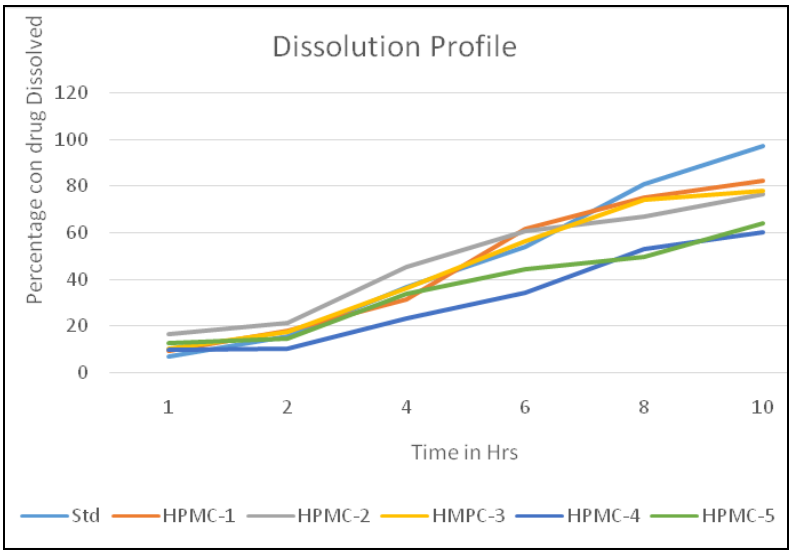

Fig 2: Comparative % dissolution profile of polyherbal SR tablets HPMC-1 to HPMC-4 with Diamicron SR tablets

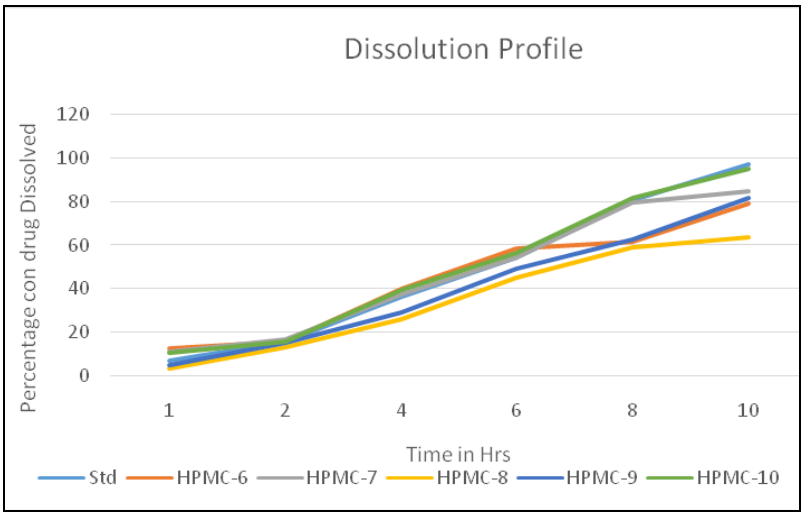

Fig 4: Comparative % dissolution profile of polyherbal SR tablets HPMC-6 to HPMC-10 with Diamicron SR tablets

Polyherbal sustained release tablet formulation with hydroxypropylmethyl cellulose (HPMC) was found to be the best in terms of dissolution profile of Polyherbal extracts when compared with the release profile of Diamicron SR Tablet. Dissolution profile of formulation showed 95.1% of drug release after 10 hours.

Conclusion

In this research work, formulation studies of the drug were carried out which includes powder properties. Sustained release tablets were prepared using mixture of hydrophilic polymers such as of HPMC K4M and HPMC K100M in various ratios. Formulated tablets were evaluated for hardness, friability, thickness, drug content and in-vitro study. HPMC -10 batch was selected as optimize batch on the basis of the cumulative drug release compared with standard Diamicron SR tablets and drug content study. Results of present study demonstrated that methodology successfully employed for formulating sustained release matrix tablets of antidiabetic polyherbal extract.

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