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DEVELOPMENT AND EVALUATION OF MULTIPARTICULATE COLON TARGETED DRUG DELIVERY SYSTEM

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ABSTRACT

A novel colon targeted multiparticles of resveratrol were prepared by solvent evaporation method, using Eudragit S-100 & Eudragit L-100 as polymer. These polymers were pH dependent so that variability in gastric emptying time can be overcome & a colon specific release can be achieved. Different combinations of polymers were selected to achieve suitable lag time for treatment of colon diseases. *In-vitro* release studies for prepared microparticles were carried out in 0.1 N HCl, 7.4 phosphate buffer and in pH 6.8 phosphate buffer. The morphology of microparticle was studied using scanning electron microscopy and it was observed that microparticle had a spherical shape and smooth surface. The percentage yield of microparticles of all formulation was in the range of 73.89% to 89.57%. The drug content determination showed that even if the polymer composition was changed the solvent evaporation process was highly efficient to give microparticle having maximum drug loading. In conclusion, the prolonged sustained release time and enhanced stability of resveratrol. *In vitro* studies revealed that multiparticles prepared have limited drug release in stomach and small intestinal environment and release maximum amount of drug in the colonic environment.

Key words: Multiparticulate drug delivery system, Microparticles, Resveratrol, Solvent evaporation method.

INTRODUCTION

During the last decade, there has been interest in developing site-specific formulations for targeting drug delivery to the colon. Colon, as a site offers distinct advantages on account of a near neutral pH, a much longer transit time, reduced enzymatic activity and a much greater responsiveness to absorption enhancers. For local pathologies of the colon, colon specific drug delivery increases the bioavailability of the drug at the target site, reduces the dose to be administered and the side effects. A local means of drug delivery could allow topical treatment of amoebiasis, inflammatory bowel diseases, colon cancer e.g. ulcerative colitis or Crohn's disease.[1]

Multiparticulate drug delivery system

Pharmaceutical invention and research are gradually more focusing on delivery systems, which enhance desired therapeutic objectives while lowering side effects. Recent trends specify that multiparticulate drug delivery systems are specifically suitable for achieving controlled or delayed release

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oral formulations with smallest amount risk of dose dumping, flexibility of combination to achieve different release patterns with reproducible and little gastric residence time. The drug release pattern from these systems depends on a carrier, which is used in the formation of multiparticulates and the amount of drug enclosed in them. Thus multiparticulate drug delivery systems provide incredible opportunities for designing novel controlled and delayed release oral formulations. The oral route is most frequently used route for oral administration of drugs. A tablet forms considerably the majority of oral dosage form due to their convenience of application and ease of preparation on an industrial scale.[2]

Microparticles

Microparticles are a type of drug delivery systems where the particle size ranges from one micron (one thousandth of a mm) to few mm. This microencapsulation technology allows protection of drug from the environment, stabilization of sensitive drug substances, elimination of incompatibilities, or masking of unpleasant taste. Hence, they play an important role as drug delivery systems aiming at improved bioavailability of conventional drugs and minimizing side effects.

Microparticulate drug delivery system is one of the processes to provide the sustained & controlled delivery of drug to long periods of time. They are small particles of solids or small droplets of liquids surrounded by walls of natural and synthetic polymer films of varying thickness and degree of permeability acting as a release rate controlling substance and have a diameter upto the range of 0.1 μm-200 μm. Microparticles are small [0.2-5 um], loaded microspheres of natural or synthetic polymers. Microparticles were initially developed as carriers for vaccines and anticancer drug.[3]

EXPERIMENTAL

Material and methods[4,5]

Resveratrol was procured from Nanjing Zelang Medical Techno Co., Ltd. China as gift sample. Eudragit RS 100, Eudragit RL 100 were obtained from Evonicdegussa, Mumbai. Methanol from Merck Specialities Private Limited (Mumbai), Dichloromethane from S.D Fine Chemicals, Mumbai, Tween 80 from Loba chemic Pvt. Ltd., Mumbai.

Preparation of microparticles

Method used: Emulsification – Solvent evaporation method

Resveratrol microparticles were prepared by modified emulsion solvent evaporation technique. The mixture containing methanol and dichloromethane (1:1 each) to which weighed amount of Eudragit S-100 and Eudragit L-100 were dispersed to form polymer solution. This dispersion was then added in water containing tween 80 (1 mL) with the help of syringe and continuous stirring was carried out at 800 rpm on mechanical stirrer equipped with 3-blade propeller. Stirring was done for 2 hrs. Agitation provided by stirrer to break the poured polymeric solution into fine droplets to form o/w emulsion. The fine droplets of drug and polymeric solution were solidified due to the evaporation of methanol and dichloromethane. The solidified microparticles were washed with distilled water and recovered by filtration. The microparticles obtained were washed with petroleum ether to remove the traces of oil

Characterisation of microparticles[6,7]

Description

The microspheres were observed for their colour, odourand appearance.

Melting point determination

Melting point of drug sample was determined by taking small quantity of drug in a capillary tube sealed at one end and was placed in digital melting point apparatus and temperature range at which the drug melts is noted.

Percentage production yield[8]

The practical percentage yield was calculated from the weight of microparticle recovered from each batch in relation to the sum of the initial weight of starting materials. The percentage yield was calculated using the following formula:

$$\% \text{ Yield} = \frac{\text{Practical mass (Microparticles)}}{\text{Theoretical mass (Polymer + Drug)}} \times 100$$

Particle size analysis[9]

Many methods are available for determining particle size, such as optical microscopy, sieving, sedimentation and particle volume measurement. Optical microscopy is most commonly used for the particle size determination.

Drug loading efficiency of resveratrol loaded microparticle[10,11]

Drug loaded microparticles (100 mg) were digested with 10 mL of methanol at room temperature for 12 h. After filtration and suitable dilution, Resveratrol present in the solution was determined at 306 nm using a UV visible spectrophotometer. Drug loading in the microparticles was estimated by using following formula:

$$L = Qm/Wm \times 100.$$

Drug content[12]

Prepared microparticles of drugs were assayed spectrophotometrically for the drug content at the maximum wavelength with proper dilution of formulations taking suitable solvent as blank.

$$\% \text{ Drug content} = \frac{\text{Practical drug content}}{\text{Theoretical drug content}} \times 100$$

FTIR spectroscopy[13]

The potassium bromide (KBr) discs with resveratrol were prepared using electrically operated KBr press Model HP-15. About 2 mg of resveratrol was triturated with about 5 mg dry KBr and then pressed into the pallet by a pneumatic press. A Jasco FTIR-5300 Fourier transform spectrometer was used to obtain IR spectra of the prepared disc of resveratrol. The scanning range was 4000-400 cm^{-1}.

Differential scanning calorimetry (DSC)[14,15]

DSC was performed in order to assess the thermo tropic properties and thermal behavior of the drug and the complex compacts prepared. About 5 mg of the sample were sealed in the aluminum pans and heated at the rate of $10^{o}C$/min, covering a temperature range of $40^{0}C$ to $300^{0}C$ under nitrogen atmosphere of flow rate 100 mL/min. Picture of microspheres were taken by random scanning.

X-ray diffraction meter (XRD)[15,16]

For characterization of crystalline state, the X-ray diffraction (XRD) patterns for Resveratrol, physical mixture of Resveratrol and other exicipents were determined using X-ray diffractometer with a copper target, at a voltage of 40 kV and current of 20 MA. The rate of the scanning was 0.30°C/min.

In vitro drug release study for resveratrol loaded microparticles

In vitro drug release studies were performed with a USP (type 2) dissolution apparatus. Samples of Resveratrol microparticles containing 10 mg of were tested in buffer solution. The rotational speed was set at 30 rpm and temperature for the dissolution medium was set at 37ºC. Samples (1 mL) were withdrawn at regular time intervals and for each withdrawal the corresponding volume was replaced with fresh buffer of the same temperature. Samples were filtered (PTFE O.45 μm) and assayed spectrophotometrically for Resveratrol at 306 nm. Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

Kinetic drug release study

The model fitting for % cumulative release was done using PCP Disso. Software to find out the best fits kinetic equation for the dissolution profile. In order to understand the mechanism and kinetics of drug release, the results of the *in vitro* dissolution study of the optimized batch of microspheres (batch) was fitted with various kinetic equation like Zero order (% release = Kt) First order (log % Unreleased = Kt), Higuchi's model (% release = Kt 0.5), Pappas Korsmeyer Equation = (% release = Ktn).

RESULTS AND DISCUSSION

Table 1: Composition of resvertrol loaded microparticles

S. No.	Batches	Drug (Resveratrol) (mg)	Eudragit S-100 (mg)	Eudragit L-100 (mg)	Emulsifying agent (%)
1	F1 (1:1)	1000	500	500	0.5
2	F 2 (1:1.5)	1000	750	750	0.5
3	F 3 (1:2)	1000	1000	1000	0.5
4	F 4 (1:1)	1000	500	500	1.0
5	F 5 (1:1.5)	1000	750	750	1.0
6	F 6 (1:2)	1000	1000	1000	1.0
7	F7 (1:1)	1000	500	500	1.5
8	F 8 (1:1.5)	1000	750	750	1.5
9	F 9 (1:2)	1000	1000	1000	1.5

Description

The sample of Resveratrol was found to –

Color: white to off-white powder

Odor: odorless

Taste: tasteless

State: fine crystalline powder

Melting point determination

After estimation it was found to be 255°C.

Table 2: Evaluation parameters of sustained release microparticles

Formulation	% Yield (%)	Drug loading efficiency of resveratrol (%)	Particle size analysis (µm)	Average drug content (%)
F_1	87.24 ± 0.565	76.45 ± 3.2	99.74 ± 2.74	71.14
F_2	82.28 ± 0.544	82.22 ± 2.7	102.97 ± 1.65	78.76
F_3	89.57 ± 0.410	86.67 ± 1.8	137.64 ± 8.23	81.36
F_4	83.14 ± 0.275	75.55 ± 2.9	117.24 ± 1.42	74.14
F_5	87.37 ± 0.06	78.92 ± 3.6	124.41 ± 9.25	76.36
F_6	79.25 ± 1.499	79.23 ± 2.3	132.56 ± 3.14	82.77
F_7	73.89 ± 0.862	78.61 ± 1.6	122.97 ± 4.65	75.35
F_8	80.45 ± 0.522	81.80 ± 1.5	130.75 ± 6.41	79.56
F_9	76.25 ± 1.803	83.42 ± 1.3	138.52 ± 4.84	89.40

Each value represents mean ± SD of three observations

IR Study

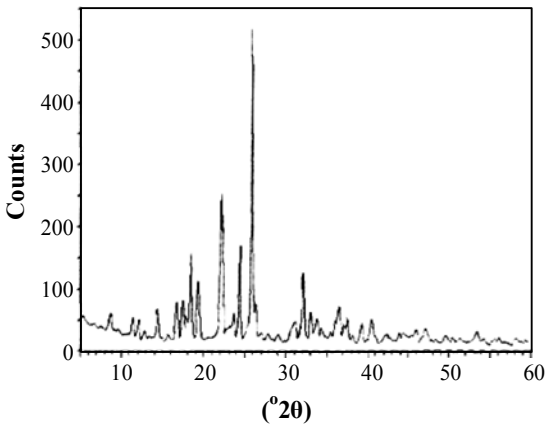

Fig. 1: IR spectra of Resveratrol

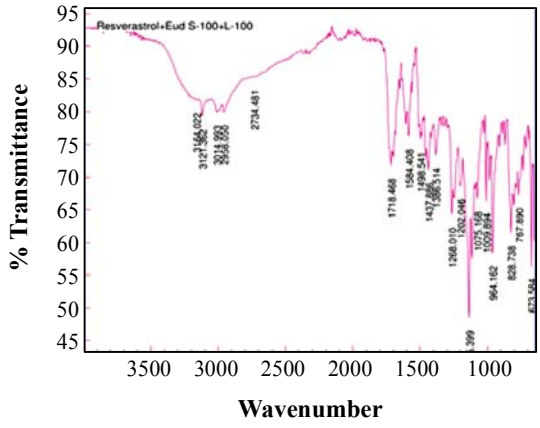

Fig. 2: IR spectra Resveratrol + Eudragit S-100 + Eudragit L-100 physical mixture

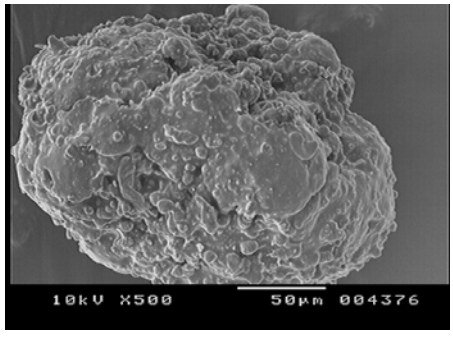

Fig. 3: Surface morphology of optimized batch (batch F3)

X-Ray powder diffractometry study

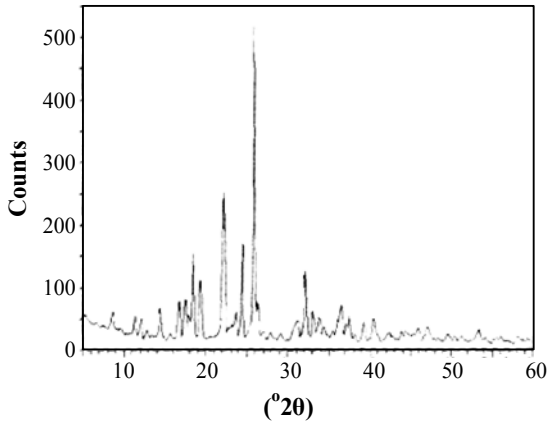

Fig. 4: XRD of Resveratrol

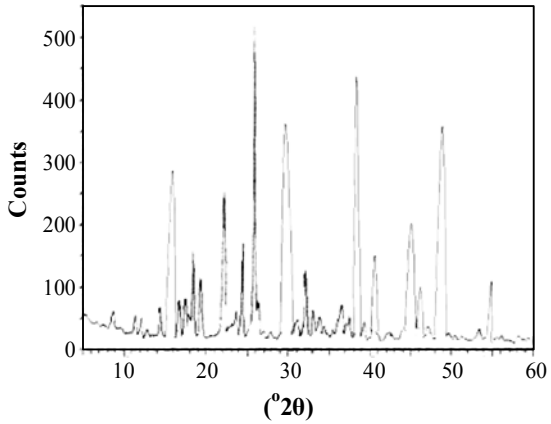

Fig. 5: XRD of Resveratrol formulation F3

In vitro drug release study for resveratrol loaded microparticles

Table 3: % *In vitro* release data of resveratrol microparticles

Time (hrs)	% CDR F1	% CDR F2	% CDR F3	% CDR F4	% CDR F5	% CDR F6	% CDR F7	% CDR F8	% CDR F9
0.5	3.44 ± 1.5	2.82 ± 0.2	3.68 ± 0.3	**1.72 ± 0.4**	**2.45 ± 0.2**	3.81 ± 0.6	6.76 ± 0.4	7.25 ± 1.2	6.26 ± 0.5
1	6.88 ± 0.2	6.02 ± 10.5	7.25 ± 0.5	**5.16 ± 0.5**	**6.51 ± 0.4**	8.36 ± 0.8	9.34 ± 0.6	11.06 ± 0.5	10.69 ± 0.8
1.5	8.73 ± 0.6	8.84 ± 0.6	9.34 ± 0.6	**8.36 ± 0.3**	**9.71 ± 0.5**	12.41 ± 0.9	12.17 ± 1.2	16.10 ± 1.7	15.36 ± 1.4
2	10.32 ± 0.9	9.71 ± 0.5	10.45 ± 0.5	**12.71 ± 0.7**	**13.15 ± 1.2**	15.24 ± 1.2	14.87 ± 1.5	17.95 ± 1.9	19.42 ± 1.5
3	11.01 ± 0.8	11.1 ± 1.5	11.37 ± 0.8	**14.1 ± 0.9**	**14.46 ± 1.4**	16.47 ± 1.3	15.83 ± 1.6	18.74 ± 1.4	21.22 ± 1.8
4	12.92 ± 1.2	12.74 ± 1.4	13.28 ± 1.2	**17.1 ± 0.8**	**17.65 ± 1.8**	17.92 ± 1.5	17.38 ± 1.5	20.93 ± 0.7	24.57 ± 1.5
5	16.56 ± 1.3	16.65 ± 1.8	16.92 ± 1.1	**22.3 ± 1.3**	**22.75 ± 1.6**	19.01 ± 1.4	18.65 ± 1.8	24.75 ± 0.8	30.84 ± 1.9
6	17.41 ± 1.5	17.32 ± 2.1	19.94 ± 1.6	**26.32 ± 1.8**	**25.63 ± 1.5**	22.31 ± 1.7	23.44 ± 1.4	27.91 ± 1.8	33.07 ± 1.4
7	32.1 ± 1.7	31.32 ± 2.6	31.76 ± 2.3	**31.3 ± 1.5**	**32.19 ± 1.9**	30.62 ± 1.8	33.68 ± 1.9	34.29 ± 2.2	35.69 ± 2.1
8	39.54 ± 1.8	48.76 ± 2.2	40.24 ± 2.1	**43.6 ± 2.3**	**55.58 ± 2.5**	57.79 ± 1.4	42.78 ± 1.8	59.80 ± 1.4	45.58 ± 2.5
9	54.5 ± 1.6	68.41 ± 2.5	62.76 ± 2.9	**63.8 ± 2.5**	**64.94 ± 2.4**	62.06 ± 2.2	55.12 ± 2.1	63.02 ± 2.5	55.12 ± 2.6

Cont…

Time (hrs)	% CDR F1	% CDR F2	% CDR F3	% CDR F4	% CDR F5	% CDR F6	% CDR F7	% CDR F8	% CDR F9
10	70.08 ± 1.9	83.7 ± 2.8	71.68 ± 1.5	**74.7 ± 2.8**	**74.65 ± 2.6**	78.97 ± 2.8	63.78 ± 3.1	79.43 ± 1.4	71.43 ± 2.8
12	88.74 ± 2.5	93.36 ± 2.5	90.58 ± 1.8	**85.04 ± 2.5**	**94.08 ± 2.3**	91.42 ± 2.5	89.56 ± 2.9	91.47 ± 2.5	86.46 ± 3.1

Each value represents mean ± SD of three observations

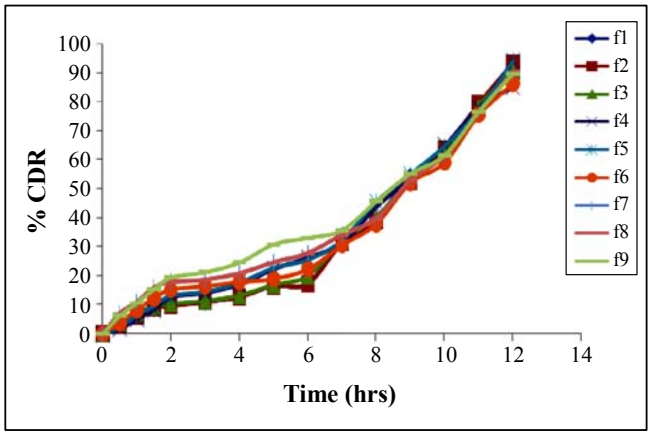

Fig. 6: Graphical representation of % *in vitro* drug release

Kinetic drug release study of Resveratrol

Table 4: Release kinetics data of resveratrol microparticles

Formulation code	Zero order	First order	Higuchi model	Hixon-crowell model	Peppas kinetics
	R^2	R^2	R^2	R^2	R^2
F1	0.933	0.885	0.846	0.828	0.838
F2	0.917	0.894	0.838	0.830	0.861
F3	0.936	0.893	0.856	0.852	0.833
F4	0.950	0.899	0.891	0.831	0.901
F5	0.958	0.891	0.893	0.877	0.870
F6	0.927	0.882	0.874	0.871	0.798
F7	0.917	0.860	0.868	0.831	0.498
F8	0.945	0.897	0.901	0.845	0.749
F9	0.959	0.895	0.935	0.868	0.712

CONCLUSION

Solvent evaporation proved best technique for the preparation of microparticles. The prepared microparticles were white and spherical in shape (SEM) with the mean particle size of all formulations

ranging between 99.74 ± 2.74 µm to 138.52 ± 4.84 µm. Optimized F_3 batch with optimum polymer concentration result in increase in particle size (137.64 ± 8.23), drug lading efficiency (86.67 ± 1.8), *In vitro* drug release rate of (90.58 ± 1.8). Release kinetics study showed that drug release from the formulation was found to follows zero order kinetic, and is by diffusion mechanism

The formulated microparticles have potential to deliver Resveratrol as colon targeted multiparticles for oral administration. The aim of this study was to explore pH dependent colon specific, multiparticulates drug delivery system for Resveratrol to treat colon cancer. Because of Resveratrol have rapid absorption and metabolism at the upper GI tract, development of a colon-specific delivery system of resveratrol becomes indispensable for the treatment of colonic diseases such as colorectal cancer, colonic inflammation etc

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