

Development and Evaluation of an Aqueous Polymeric Dispersion of Eudragit L 100-55 Using Emulsification Technology

Research Article

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Abstract

Aqueous polymer dispersions (APD) are preferred on environmental and safety grounds. APD offer several advantages over polymers dissolved in organic solvents including lower spraying viscosities, higher solids loading, higher spray rates, no solvent environmental, toxicity, or flammability issues, and reduced energy requirements. The purpose of this work is to prepare and characterize an aqueous-based pseudolatex dispersion of Eudragit L100-55 using emulsification technology with superior stability. The prepared APD is evaluated on the basis of organoleptic, physical, chemical and in-vitro drug release performance. APD film is prepared by casting method and evaluated. Coating is done over Diclofenac sodium tablet and In vitro drug release profile of APD coated tablet and organic coated tablet is studied and shows better release in case of APD as compared to market formulation and organic coating.

Key Words: Aqueous Polymeric Dispersion (APD); Emulsification Solvent Evaporation; Latex; Pseudolatex; TEM; DSC.

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Introduction

Coating with water insoluble polymers is an important technique for targeted or controlled release formulations and the taste-masking of drugs, during which the aqueous polymer dispersions are widely used as an alternative to an organic polymer coating system [1]. Water soluble polymers are always being in good demand because of their certain advantages over organic solvents with respect to ecological, toxicological and manufacturing safety concern, high cost of organic solvents, solvent toxicity [2]

Aqueous polymeric dispersions, latexes, or pseudo latexes are all colloidal systems in which high molecular weight polymers are homogeneously dispersed in submicron sizes with the aid of surfactant(s) and other stabilizing agents. aqueous dispersion containing hydrophobic material that are useful as reduced volatile content may be used as a coating, resin, or an additive [3]

Types of aqueous polymeric dispersion

Aqueous polymeric dispersions that are widely used by the pharmaceutical industry are manufactured using different processes and different starting materials. They are classified into:

- *Latex*

Latexes are aqueous polymeric dispersions produced by emulsion polymerization. The homogeneous and heterogeneous nucleation models have been proposed to describe such processes. As a direct outcome of the manufacturing process, latex may contain not only polymers, but also surfactants, as well as traces of initiators and monomers that must be eliminated as completely as possible from the lattice used in pharmaceutical applications [4,19,20].

- *Pseudo latexes*

Pseudo latexes are prepared by dispersion of the bulk polymer in an aqueous medium. The pseudolatex dispersion, a coating formulation often includes plasticizers to enhance the flexibility of the film and facilitate polymer sphere coalescence, antiadherents to prevent substrate agglomeration during both the coating process and storage, surfactants to promote spreading of the atomized droplets on the substrate surface, and pigments. The addition of other excipients can significantly impact the physical stability of the dispersion, drug release, and film quality [5,19,20]. An APD can be prepared in two different forms:

- a. Ready to use: milky white liquid
- b. Freeze dried / spray dried: powdered

Different techniques used in APD

Water insoluble polymers can be converted into aqueous dispersions by emulsion polymerization, emulsion solvent evaporation, phase inversion, or solvent change method.

• *Emulsification technique*

Emulsification polymerization

- » Direct Emulsification/ emulsion solvent evaporation
 - » Self Emulsification
 - » Phase Inversion Emulsification or Solvent change method
1. Nanotechnology
 2. pH modification
 3. Phase separation/ coacervation

Materials and Methods

Materials

Eudragit L100-55 was received as a gift sample from Evonik industries, Mumbai. Diclofenac sodium was purchased from Omega pharmaceuticals, India and Poloxamer 407 & Sodium lauryl sulphate (SLS) were supplied by Central Drug House (P) Ltd., Mumbai. All other chemicals were of either reagent or analytical grade as received.

Table 1: Different types of emulsification

Properties	Direct	Inversion	Self
Definition	The liquid polymer in a volatile organic solvent is emulsified in water that contain emulsifier & stabilizer by using conventional emulsification method [7]	The liquid polymer in an organic solvent is compounded with long fatty acid with conventional rubber mixing equipment. Water in polymer inverts to polymer in water emulsion. Phase inversion is complete, which means that all water molecules in the system are transformed to be continuous phase at the phase inversion point [8]	Polymer molecules are modified chemically by the introduction of basin or acidic group & self emulsification occurs [6]
Droplet size	1 µm or larger	0.8-1µm or larger	Small as 0.1µm
Ease of preparation	Easy to prepare	Require great care and control	Not easy to prepare
Cost	Economic	Expensive	Expensive
Example	Eudragit	Polyacrylamide & its co- polymer [9]	

Table 2: Formulation of different concentration of APD

Ingredients	Example	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Polymer(g)	Eudragit L 100-55	0.5	1	1.5	2	2.5	3	3.5	4.0	4.5	5	6
Organic solvent(ml)	Acetone	20	20	20	20	30	30	30	30	30	30	30
Stabilizer(%w/w)	Poloxamer 407	6	6	6	6	6	6	6	6	6	6	6
Surfactant(%w/v)	SLS	1	1	1	1	2	2	2	2	2	2	2
Aqueous phase(ml)	Distilled water	50	50	50	50	50	50	50	50	50	50	50

Development of an APD

Several formulations were developed using the emulsification methodology. Solvents for the organic phase was acetone, SLS was taken as surfactant and poloxamer 407 as stabilizer [10,15,16,17,18].

The Eudragit L100-55 dispersion was prepared by emulsion solvent evaporation method. Accurately weighed Eudragit L100-55 was dissolved in acetone, and the resulting solution was dispersed in 50 ml of aqueous phase having surfactant and stabilizer, at room temperature using a Mechanical stirrer (Hicon Instrument Manufacture Co. Ltd. India). The type of the emulsion was determined by diluting the emulsions with either water or acetone. Then the emulsion was subjected to rota evaporator (Perfit, India). To optimize the formulation various batches were made which is given in Table 2.

Pseudolatex (APD) characterization

- » *Organoleptic characterization:* On the basis of color, odour and appearance APD was characterized [11]
- » *Viscosity:* Viscosity was measured with a Brookfield DV III Ultra programmable rheometer at 20°C, 30 rpm [11,12,13].
- » *Differential scanning Calorimeter (DSC):* DSC study is done for the authentication of the drug [14].
- » *Particle size distribution:* It is measured by zeta sizer instrument Malvern Instrument outsourced from Jamia Hamdard [14].
- » *Scanning electron microscopy:* Scanning electron microscopy has been used to determine the surface morphology and texture. SEM studies were carried out by using Zeiss scanning microscope [16,17].

- » *Transmission electron microscopy*: Transmission electron microscopy has been used to determine the surface morphology and texture[18,19].
- » *Zeta Potential*: Zeta potential is measured by zeta potential analyzer outsourced from Jamia Hamdard[14,20].
- » *Solid content (wt%)*: The solid content of the dispersion was measured as follows: an accurately weighed amount of the dispersion (about 1 g) was spread on a disc and dried for at least 3 h at 110°C to constant weight (according to Ph. Eur. 2.2.32d). The solid content (wt%) was the ratio of the dried residue weight to the original weight of the dispersion[21,22].

$$\% \text{solid Content} = \frac{\% \text{solid Content}((\text{Weight of dish} + \text{residue}) - \text{Weight of dish})}{(\text{Weight of sample})} \times 100$$

- *In vitro drug release*

The dissolution test for APD coated tablets was performed according to USP (USP 2007) adopting method B in pH 1.2 and pH 6.8 buffers. Drug release was measured in a USP dissolution bath using apparatus II at 50 rpm. In the first stage (pH 1.2); the tablets were putted in 900 ml of 0.1 N hydrochloric acid in a USP dissolution bath equilibrated to a temperature of 37±0.5°C. The paddle stirring rate was set at 50 rpm. Six tablets were introduced into the apparatus and the apparatus was run for 2 h. After the operation outlined above, an aliquot of the fluid was drawn, and the second stage (pH 6.8) was commenced. This last consisted of a phosphate buffer of pH 6.8 prepared by mixing 0.1 M hydrochloric acid with 0.20 M tribasic sodium phosphate (3:1). The apparatus was operated for a further 45 minutes. At the end of the time period, an aliquot of the fluid was drawn. Samples were as sayed by UV method, at 273.4 nm wave length [23,24].

The following characteristics were determined for a dispersion obtained with a good yield, i.e. which formula could be used for an industrial scale-up. The pH was determined by using a pH meter.

Evaluation of APD film

For the development of APD film 10% concentration of TEC was optimized as plasticizer. APD film was evaluated on the basis of physical parameters e.g, weight, thickness, folding endurance, percentage moisture uptake and percentage moisture content.

- *Physical appearance*

The films were observed visually for their completeness, uniformity, surface texture and flexibility.

- *Moisture Content*

The prepared films were marked, then weighed using shimadzu (AU x 220) digital balance individually and kept in a desiccators containing activated silica at room temperature for 24 h. The films were weighed again and again individually until it showed a con-

stant weight. The percentage moisture content was calculated as a difference between initial and final weight with respect to final weight

- *Percentage Moisture Uptake*

A weighed film kept in desiccators at normal room temperature for 24 hours was taken out and exposed to 84% relative humidity (saturated solution of potassium chloride) in desiccators until a constant weight for the film was obtained. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight (Arora et al., 2002).

- *Thickness*

The thickness of the film was measured at three different points using a micrometer screw gauge and average thickness recorded.

- *Folding Endurance*

Folding endurance was determined by repeatedly folding the film at the same place until it broke. The number of times the film could be folded at the same place without breaking was the folding endurance value.

Result and Discussion

DSC of drug

DSC study shows the melting point of the dug at 284.9°C which is corroborated with the literature value.

FTIR study

The FT-IR of the drug is shown in fig 2 whereas the APD coating is shown in fig 3. which shows that the drug is coated with APD

HPLC method for diclofenac sodium

- a. Equipment: Shimadzu HPLC with an attached UV detector.
- b. Column: C18 reversed- phase column (25 cm ×4.6 mm, particle size 5µm)
- c. Mobile phase: Acetonitrile: water (60:40)
- d. Flow rate: 1 ml/min.
- e. Detection: UV, 273.4 nm
- f. Injection: 20 µl

The calibration curve of Diclofenac was prepared by HPLC method for the determination of drug content and in vitro analysis. The HPLC chromatogram of drug is shown in fig. 4

APD Development

During preliminary studies, several surfactants were studied as stabilizers for the preparation of the pseudolatexes. Using cetyl alcohol as the stabilizer, the produced pseudolatexes were converted into gel-like substances within one hour. A stable dispersion was obtained with poloxamer 407 (Pluronic F 127) given in table 3.

Figure 1: DSC of drug (Diclofenac sodium)

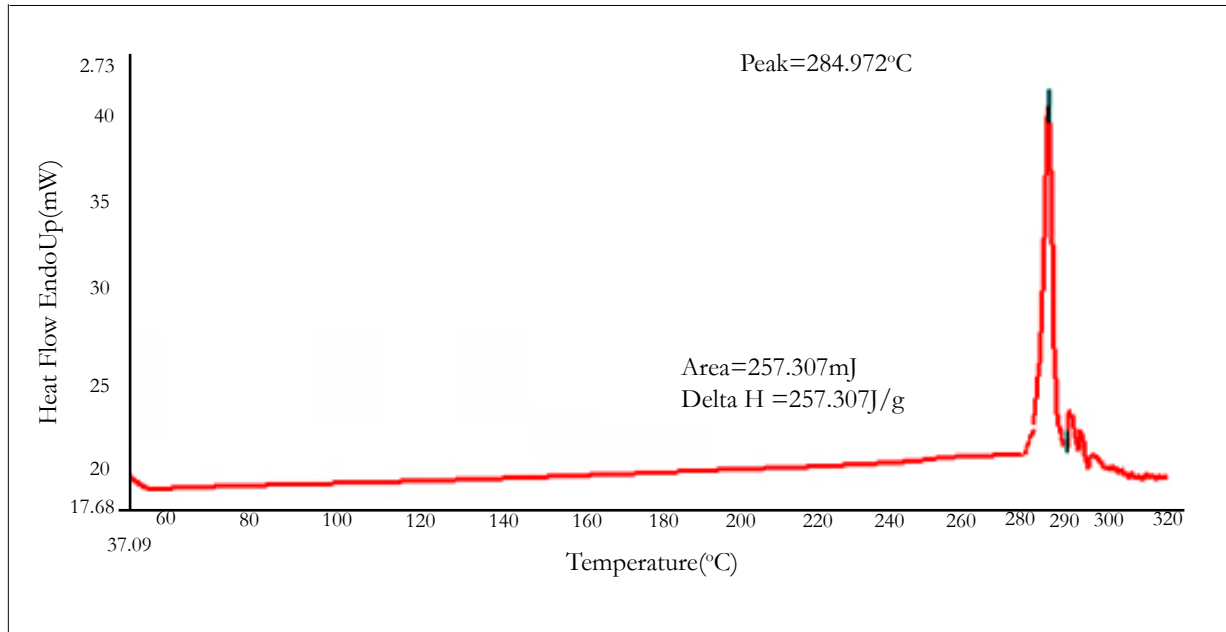


Figure 2: FT-IR spectrum of Diclofenac sodium

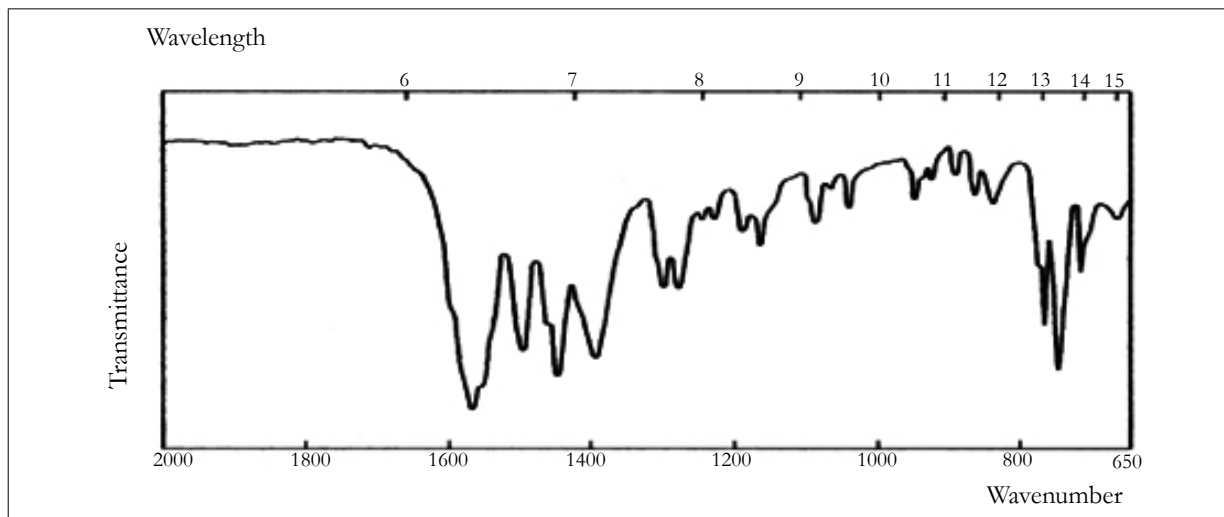


Figure 3: FT-IR spectrum of APD coating

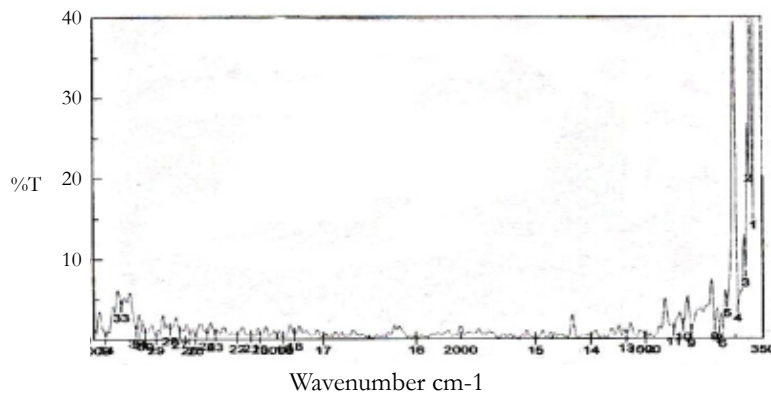


Figure 4: HPLC chromatogram of Diclofenac sodium in mobile phase

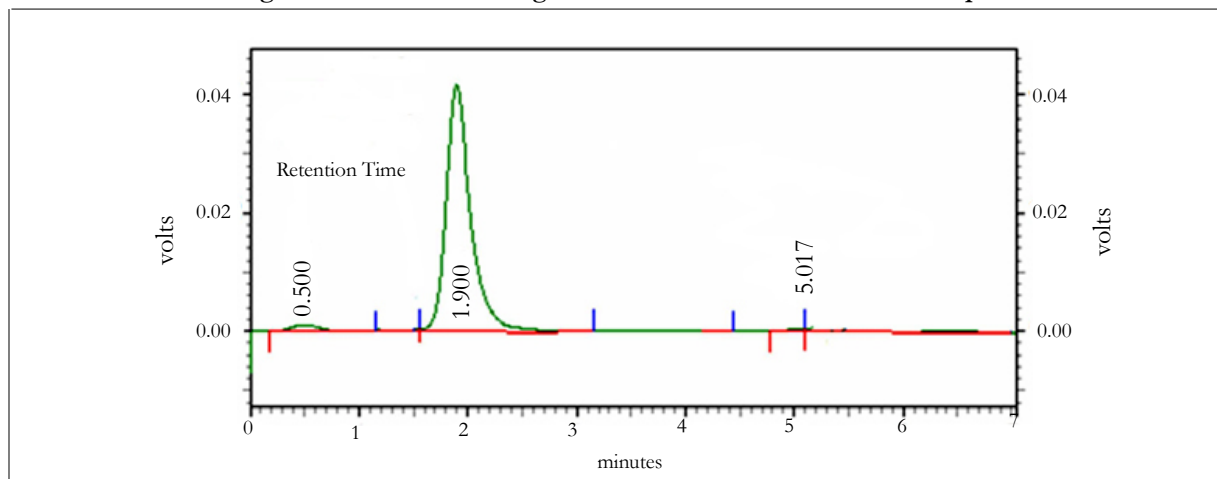


Table 3: Formula for 10%APD (F10)

For 10% APD		
Ingredients	Example	Quantity
Polymer	Eudragit L 100-55	5 g
Organic solvent	Acetone	30 ml
Stabilizer	Poloxamer 407	6 % w/w
Surfactant	Sodium lauryl sulphate	2 % w/v
Aqueous phase	Distilled water	50 ml

Characterization of APD

- *Transmission Electron Microscopy(TEM)*

TEM image shows the sphericity of the APD developed and the smoothness of the surface texture as shown in fig 5.

- *Particle Size and Zeta Potential*

The stability of the dispersions was found to be dependent

on the amount of poloxamer 407 (wt% of the polymer). The particle size decreased significantly on increasing the amount of Poloxamer 407, while no significant changes were observed above 6%. Increasing the amount of poloxamer 407 produced little change in the zeta potential. The final optimized dispersion (solid content percentage about 15.9%) was obtained with an average particle size of 611 nm given in fig 6 (A), and a pH of 3.50. A zeta potential of -30.3 mV was measured given in fig 6(B).

Evaluation of film

The physical evaluation of the developed APD such as thick-

Figure 5: TEM photograph of 10 % emulsion

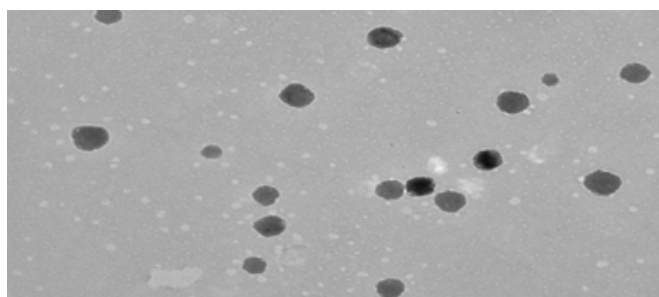


Figure 6: (A) Zeta potential

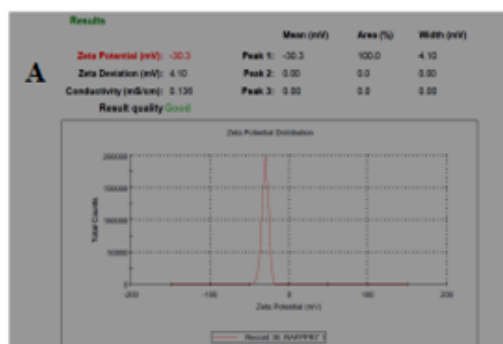


Figure 6: (B) Particle size of 10 % aqueous polymeric dispersion

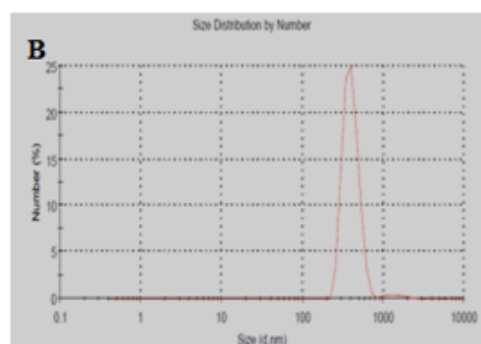


Figure 7: Comparative % release profile for different concentration of APD

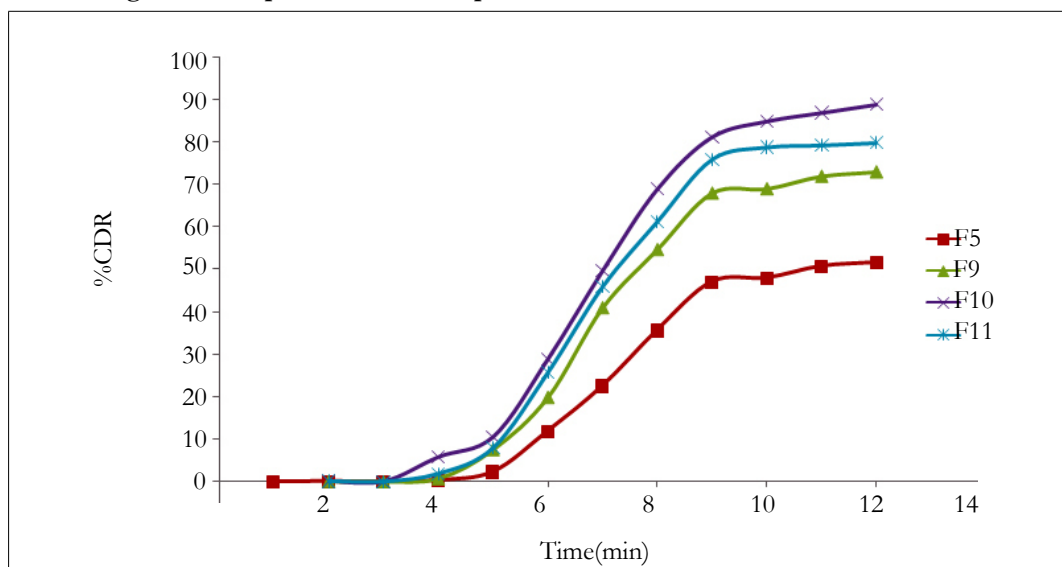


Figure 8: Comparative drug release profile

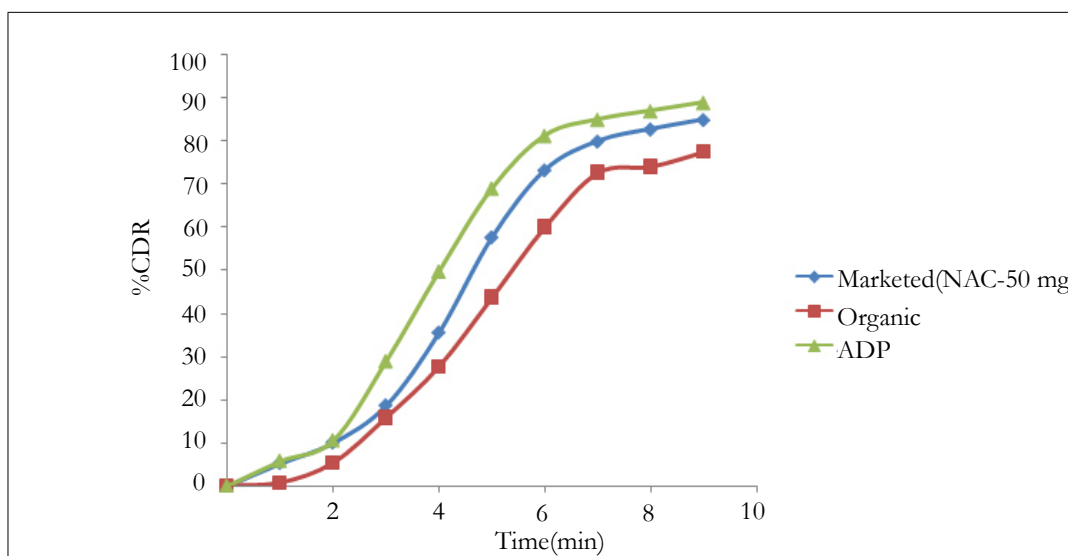


Table 4: Physical Parameters of APD film

S.No.	Weight (mg)	Thickness (μ)	Folding endurance	% moisture uptake	Moisture content
1	22.4	131	230	15.90	4.00

Table 5: Model fitting of the drug release profile

Formulation	Zero Order Equation R2	First Order Equation R2	Higuchi Equation R2	Korsmeyer Peppas Model R2
F10	0.936	0.958	0.877	0.951

Table 6: Stability study of APD

S. No.	Time in month	pH	Viscosity	Appearance
1	1	3.60	8.0	No agglomeration
2	2	3.60	8.0	No agglomeration
3	3	3.71	8.2	No agglomeration

ness, moisture content, moisture uptake as well as folding endurance is given in table 4.

Drug release

The drug release profile of the different APD is given in fig 7 whereas comparative release profile of the optimized APD with

respect to the marketed as well as organic based polymeric dispersion is given in fig 8.

Drug release kinetics

Model fitting of drug release profile is shown in table 5. The high R2 value is near to unity and is maximum that is 0.958 in case of first order for optimized APD. So its follows the first order kinetics. The slope(n) in case of korsmeyer peppas model was

found to be more than 0.5 which further suggest non- fickian diffusion method.

Stability studies

The optimal formulation was evaluated for stability studies by storing at 40 degree Celsius at 75% RH & tested for 3 months. The APD was analyzed for physical parameters given in table 6. The dispersion was stable and no sedimentation occurred after 3 month storage

Conclusion

APD of Eudragit L100-55 was prepared by the emulsification technology (emulsion solvent evaporation method) using Poloxamer 407 as the stabilizer and SLS as a surfactant. A stable dispersion was obtained through the optimization of surfactant and stabilizer. The optimized concentration of stabilizer and surfactant was 6% w/w of polymer and 2% w/v, respectively for Eudragit L-100-55 dispersion. Different concentration of APD was prepared and evaluated.

On the basis of Organoleptic properties, chemical characterization and in vitro drug release performance formulation F10 (10% APD) was found to be better than the other formulations. Organoleptic and chemical characterization included appearance, odour, pH, viscosity, particle size-shape, zeta potential and % solid content. Appearance of 10% APD was milky white and pH was 3.5. Viscosity was 8.0 mPa.s measured by Brookfield rheometer using 3no.spindle, 30 rpm. Particle surface morphology was done by SEM analysis. Particle size was measured by zeta sizer and was found to be 611 nm. Zeta potential of the optimized APD was -30.3mV. The present dispersion exhibited superior stability with regard to temperature and pH changes. The evaluation parameters of the free film were well controlled by the plasticizer concentration.

Formulation of uncoated tablet of Diclofenac sodium was done by wet granulation method. Enteric coating was successfully done using 10 % aqueous dispersion of Eudragit L 100-55. In vitro drug release of 10% APD was 88.95%. In vitro drug release of APD coated tablet was higher than organic coated tablet. FTIR and UV studies did not show any evidence of interaction between the drug and the polymers. The preparation of this aqueous dispersion is easy and requires short time which decreases the cost of the coating process. The results of the present study suggest that the aqueous-based dispersion of acrylic polymers can be used in a wider variety of conditions for coating.

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