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Research Article

Pre-formulation, Studies of Multiple Unit Pellet System Aspirin Matrix Tablet

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ABSTRACT

The present work aimed preformulation studies for sustained release multi unit particulate tablet of Aspirin. Peripherally, acetylsalicylic acid acts by inhibiting the synthesis and release of prostaglandins. Migrates into the blood within 15 minutes and reaches the maximum concentration in the blood within 2.1 hours after intestinal absorption and the blood concentration half life is as short as 3.1 hours. Decreasing the dose frequency of Aspirin increases patient compliance and also improves the efficacy of contained drug, hence; hasten the cure from the indication. Therefore, MUPS tablet was prepared to control the release of Aspirin over a prolong period of time as multi unit particulate system are familiar, proven, easy to formulate and economical.

Key words: MUPS, Aspirin, Preformulation, Matrix tablet, Pelletization

INTRODUCTION:

Aspirin also known as acetylsalicylic acid, is a salicylate drug, often used as an analgesic to relieve minor aches and pains, as an antipyretic to reduce fever, and as an anti-inflammatory medication [1]. As with other NSAIDs, combinations of aspirin and caffeine provide slightly greater pain relief than aspirin alone. In recent years, Multiple Unit Pellet Systems (MUPS) tablets [2] are widely used in solid dosage form design. MUPS is considered to provide pharmacokinetic advantages compared to monolithic dosage forms. Typically, modified release pellets are contained in MUPS tablets.

The compression of multiparticulates into tablets, unlike the hard gelatin capsule, is a tamper-proof dosage form and has greater physicochemical and microbiological stability of pellets [3] as they are embedment in the inert matrix.Tablets have less difficulty in esophageal transport than capsules. Tablets containing coated subunits can be prepared at a lower cost than these subunits filled into hard gelatin capsules because of higher production rate of the tablet press. The expensive control of capsule integrity after filling is also eliminated. In addition, tablets containing multiparticulates without losing the controlled-release properties could be scored, which allow a more flexible dosage regimen.Composing the tablet with equal or different kinds of particles can be combined and so that very specific release profiles can be generated.Once the coated subunits have been developed different dose strengths can be prepared just by varying the tablet size keeping the same composition – no additional development efforts need to be taken. Another option for dose strength variation is the development of dividable multi-unit tablets. Since the release characteristics are related to the single subunits, dividing the tablet does not affect the release characteristics as it is true for monolithic tablets [4, 5]. Rapid and uniform transit of subunits contained in tablets from the stomach into small intestine owing to their small size, drug release is more uniform and possibility of dose dumping is avoided with minimized tendency for inter-subject variations.

Rapid but uniform transit of micro pelletscontained in MUPS from the stomach into smallintestine owing to their small size and thus lesserpossibility of localized irritation, better and moreuniform drug absorption and greater bioavailability [6].Uniform emptying of micro pellets from stomach into small intestine facilitates rapid dissolution of enteric coating and drug release resulting in early tmax and C_{max}(peak time and peak plasma concentration) in case of delayed-release formulations

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[7]. In case of controlled-release preparations, drug release is more uniform and possibility of dose dumping is avoided with minimized tendency for inter-subject variations.

MUPS with matrix pelletsused generally in controlled release formulations. These pellets are coated with swellable or erodable polymers than diffusible polymers [8]. The main problem of matrix pellets in compression is fusion of polymer coating of pellets with other pellets and also polymer coating with extra-granular material. This can be counteracted by coating with any non interfering coating agent.

Application of MUPS:

To protect drugs that are unstable in acid from disintegrating in the gastric juice e.g. antibiotics enzymes, peptides proton pump inhibitors. pH Dependent controlled release of drugs for optimal absorption. GI targeting of different sections of small intestine or of the colon (absorption window, targeting localized effects).

Colon targeting for local treatment and systemic therapies [9]. The key to controlling the release of the drug is the pH dependent dissolution of the film coating, which takes advantage of the different pH values that exist along the gastrointestinal tract. Since the coatings dissolution is controlled by pH, or by gradually permeability, the drug is release in a precise manner in specific sections of the digestive tract, or at specific times after intake.

Acetyl salicylic acid [10] was selected as a model drug. It is generally known that aspirin. Migrates into the blood within 15 minutes and reaches the maximum concentration in the blood within 2.1 hours after intestinal absorption and the blood concentration half life is as short as 3.1 hours. Since aspirin is quickly absorbed in and excreted from blood, it is difficult to maintain in the therapeutic level for a long time, for this reason currently commercially available aspirin tablet must be taken 3 times a day. Oral administration of aspirin often includes various side effects including increase the risk of gastrointestinal bleeding. Therefore there is a strong need for the development of long acting aspirin preparation which is capable of exhibiting the effect in a most safe and efficiency manner over an extended period of time.

Tablets are indeed the most popular solid dosage form for oral administration. One category of tablet formulations that has gained remarkable importance in drug therapeutics owing to various benefits it offers is controlled or modified release formulations. Controlled release capsules often containing plurality of coated pellets is yet another category of solid oral formulation that offers analogous therapeutic benefits. A relatively more recent approach that has come into existence is the one that combines the features of both controlled release tablets and modified release capsules in one dosage form. Such a system is known as MUPS tablets. MUPS is abbreviation for Multiple-Unit Pellet System. However, from pharmaceutical industry and research perspective, the term in general refers to MUPS compacted into tablets. Thus, the resulting tablets prepared by compaction of modified release coated multiparticulates or pellets are called as MUPS. Compaction of MUPS is a challenging area. Aggressive research but by few individuals and industries is being carried out worldwide in this area.

MATERIALS AND METHODS:

Material

Table 1:

Sr. No.	Name of Excipients	Manufacturer/supplier
1	Aspirin	SD fine Mumbai
2	Celesphere 203	Alkem Research Lab Mumbai
3	Eudragit L	Evonik Industries
4	Hypromellose 2910 (6 cps)	Colorcon, Mumbai.
5	Hypromellose 2910 (15 cps)	Sai MirraInno Pharma
6	Eudragit RS	FMC biopolymer, Mumbai
7	Magnesium stearate	FMC biopolymer, Mumbai
8	Talc	Homedicines
9	Aerosil	Chemco , Rajkot
10	Crosspovidone	Signet Corporation, Mumbai
11	Polysorbate 20	SD fine chemicals Mumbai
12	Sodium hydroxide	Amexin Pharma, Mumbai
13	Iso propyl alcohol	Ranchem , New Delhi
14	Hydrochloric acid	Chemco, Rajkot

Table 2: Instruments:

Sr. No.	Instrument	Source
1	Fluidized Bed Coater	Alliance, Bombay
2	Electronic Analytical Balance	Shimandzu, Japan
3	pH-meter	Hanna Instrument, Mumbai
4	Stirrer	Cadmach, Vatva
5	Differential Scanning Colorimeter	Perkin Elmer Instrument Pyris-1
6	Single Head Rotary Tablet Machine	Cadmach,Bavla
7	VernierCalliper	Hanna Instrument, Mumbai
8	Hardness Tester	Pfizer Tester,
9	USP Dissolution Apparatus II	Scientific USP standards DA60s

PREFORMULATION STUDIES:

Identification of Drug:

Infrared Spectroscopy Study:

The powder of Aspirin and KBr were prepared using hydraulic pellet press at a pressure of 7 to 10 tones. FTIR [11] was scanned from 400-4000cm^{-1} by using perkin Elmer spectrum GX FTIR. FTIIR study was carried out individually for drug, each polymer and finished product (tablet) compared Aspirin FTIR spectra of pure drug and polymer.

Analytical Methods

Determination of analytical wave length[12]:

A standard stock solution of aspirin in 0.1N Hcl was prepared having a concentration 600 µ g/mL. A 5.0 mL portion of stock solution was further diluted Aspirin water in a 100.0 mL.volumetric flask up to mark to get final concentration 30 µg/mL. The standard solution of aspirin (30 µg/mL) was scanned in the range of 400-200 nm.in 1.0 cm cell against solvent blank and spectra was recorded , the absorbance maxima was observed at 258.0 nm.

Melting Point Study:

The melting point study was carring out Aspirin the help of capillary method or Differential scanning colorimetry (DSC) [13].

Standard Calibration Curve:

Standard Calibration Curve of Aspirin in 1.2 pH Buffer:

Stock solution of Aspirin was prepared by dissolving 50 mg of drug in 200 ml of 6.8 phosphate buffer. Aliquots of 1,2,3,4,5,6 ml (5 to 30 µg/ml) were transferred separately in to 50 ml volumetric flasks from the stock solution. Volume was adjusted up to the mark Aspirin the same solvent. Absorbance of the above solutions was taken at 272 nm against the blank. Graph of absorbance Vs concentration was plotted [14].

Drug – Excipient Compatibility Study:

Compatibility of excipient Aspirin drug was studied by DSC or FTIR

***FTIR*:**

Physical mixtures of drug and polymer were filled in the prewashed ampoules and sealed. The sealed ampouleswere kept at 40±5^{0}c/75 %RH for 30 days in stability chamber. At the end of 30 days ampoules were removed from stability chamber and proceed for interaction study [13]. Drug polymer interaction study was done by using FTIRIR. In this study thermogram of pure drug, mixtures of drug: HPMC, drug: eudragit RS, drug: Eudragit L was taken.

Physical Parameter:

a) Solubility

Solubility is a useful parameter mainly for poorly soluble drugs. Bioavailability problems are often present, when the solubility of a drug is less than 10 mg/ml over the pH range 1-8. Drug solubility was determined by preparing saturated drug solutions in various buffer medium, maintained at 37°C ± 0.5°C in a water bath and continually shaken in to mechanical shaker (Remi mechanical shaker, Bombay) up to 24 hrs. spirin drawn samples were filtered through a filter paper, and assayed by UV spectrophotometer [15].

b) Flow Property

Bulk density, tapped density, compressibility index, Hausners ratio of API were presented under chapter preformulation study [12,15].

c)Particle size Measurement

Particle size analysis was carried out by malvonizer apparatus andsieve analysis method [16].

RESULT AND DISCUSSION:

Table 3: Organoleptic Characterization of Aspirin:

Sr. No.	Parameter	Result
1	Color	A white to off white Amorphous powder
2	Odour	Characteristic
3	Taste	Slight bitter

Identification of Drug:

By Infrared Spectroscopy: The Infra Red absorption spectrum of the finely ground sample in KBr dispersion compressed into a disc should exhibit maxima only at the same wavelengths as that of a similar preparation of working standard.

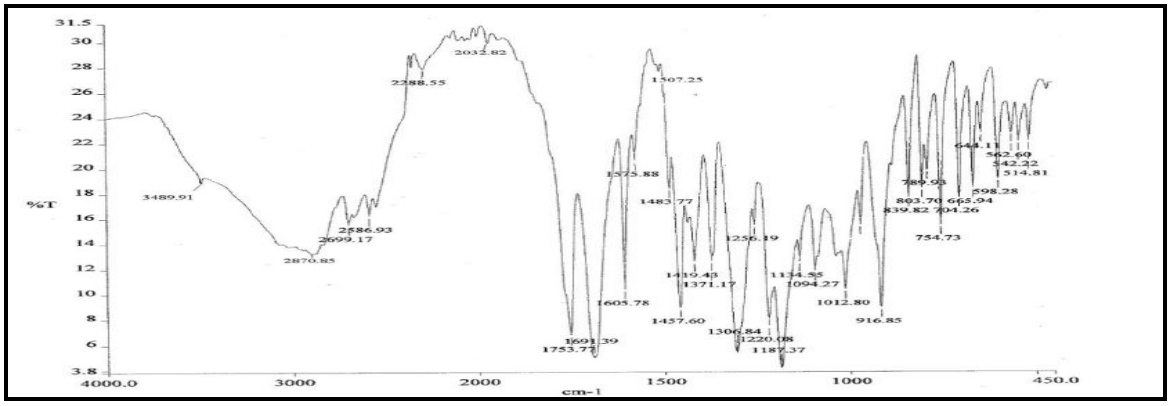

Figure 1: IR spectrum of Aspirin

Table 4: Wave number of functional groups of Aspirin

Sr. No.	Wave number	Functional group
1	1600-1400 cm^{-1}	C=C (Aromatic)
2	1750-1730 cm^{-1}	C=O (ester)
3	1725-1700 cm^{-1}	C=O (carboxylic acid)
4	1300-1000 cm^{-1}	C-O (ester/carboxylic acid)
5	3300-2500 cm^{-1}	O-H (carboxylic acids)

The above peaks can be considered as characteristic peaks of Aspirin

Analytical Methods:

Determination of analytical wave length:

A standard stock solution of aspirin in 6.8 phosphate buffer was prepared having a concentration 600 µg/mL. A 5.0 mL portion of stock solution was further diluted Aspirin water in a 100.0 mL.volumetric flask up to mark to get final concentration 30 µg/mL. The standard solution of aspirin (30 µg/mL) was scanned in the range of 400-200 nm.in 1.0 cm cell against solvent blank and spectra was recorded , the absorbance maxima was observed at 272.0 nm.

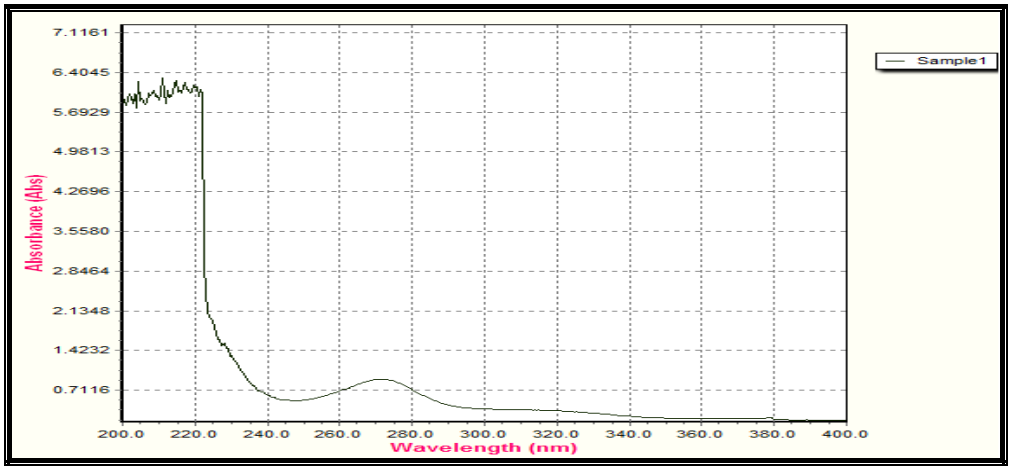

Figure2: UV spectrum of Aspirinin 6.8 phosphate buffer

X-ray Diffraction ofAspirinPattern:

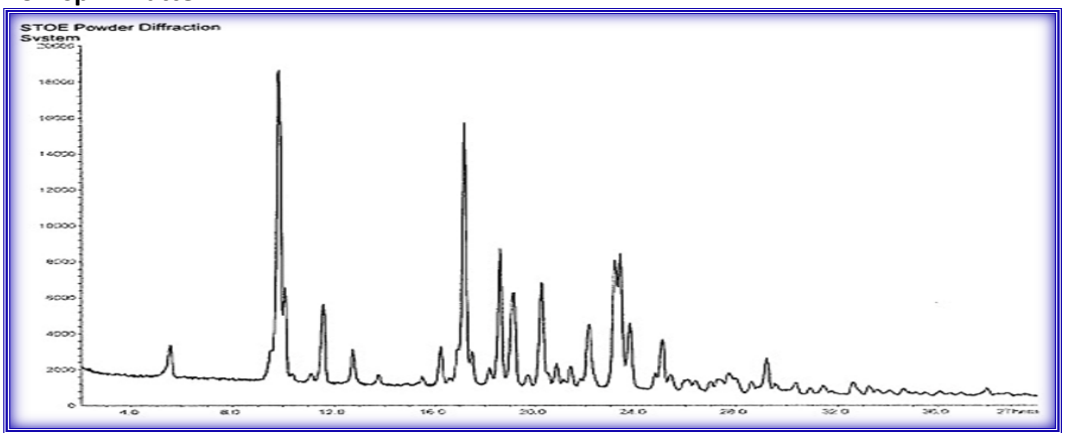

Figure 3: **X-ray powder diffraction pattern of Aspirinin crystalline form**

Melting Point Study

Table 5: The DSC test was done onAspirin was presented below

Sl. no	Stage	Temperature
1	Onset	125.76^0c
2	Peak	137.25^0c
3	End set	142.84^0c

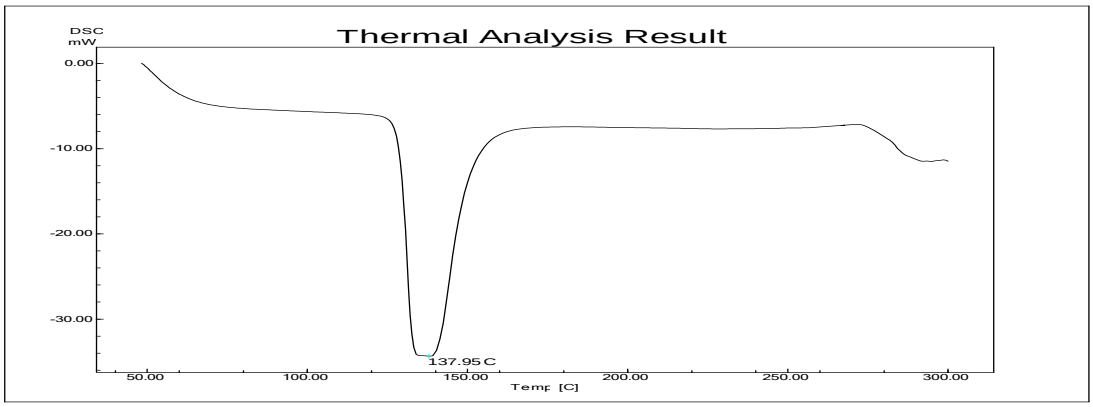

Figure 4: Thermal Analysis result of Aspirin

Particle Size Analysis: Particle size of drug was determined by Malvern particle size analyzer.D (10, 13.42), D (50, 55.32), D (90, 149.21).

Table 6: Micromeretics Properties ofAspirin

Drug	Angle of Repose (ɵ)	Bulk Density(g/ml)	Tapped Density(g/ml)	Carr's Index(%)	Hausner's Ratio
Aspirin	27.34	0.375	0.516	27.32	1.37

From the Results of Preformulation studies of the API, It was concluded that Aspirin has poor flow property and compressibility property. So, to improve the flow and compressibility property, it was beneficial to use the directly compressible grade components in the formulation of tablet.

Drug excipients compatibility study:

FTIR Analysis result of Drug + HPMC 6cps:

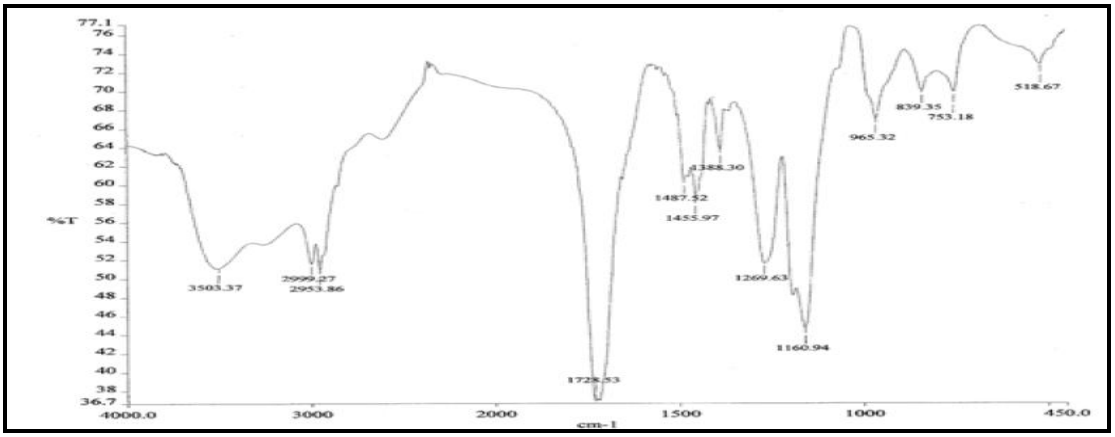

Figure 5: FTIR Analysis result of Drug + HPMC 6cps

FTIR Analysis result of Drug + Eudragit RS:

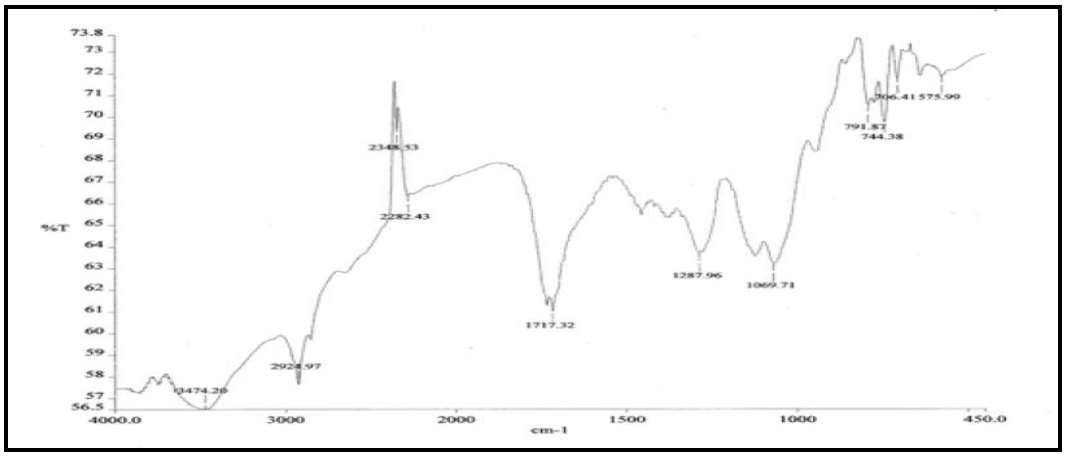

Figure 6: FTIR Analysis result of Drug + Eudragit RS

FTIR Analysis result of Drug + Eudragit L

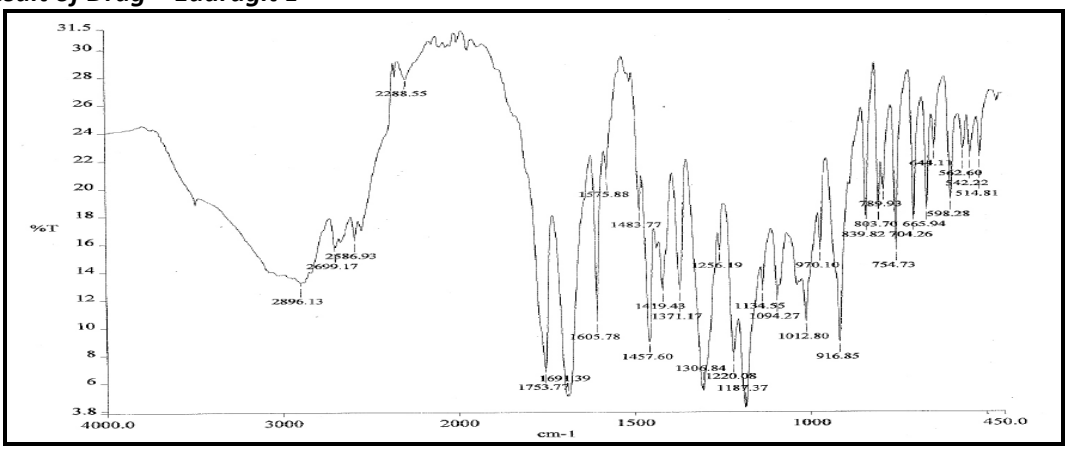

Figure 7: FTIR Analysis result of Drug + Eudragit L

From the above FTIR Study and physical observation it was concluded that there was no significant Drug- Excipients interaction was observed. The results of FTIR study shown that there is no change in drug's melting peak after the preparation of tablet. So we can conclude that drug and other excipients are compatible which each other.

Analytical Method Development

Calibration curve ofAspirin:

Calibration curve for Aspirin was taken in 6.8 Phosphate buffer.

Table 7: Absorbance at different concentration of Aspirin

Sr. No.	Concentration (µg/ ml)	Absorbance			Avg. Absorbance
		A_1	A_2	A_3	
1	0	0	0	0	0
2	5	0.198	0.186	0.189	0.191
3	10	0.351	0.359	0.352	0.354
4	15	0.534	0.530	0.526	0.530
5	20	0.688	0.687	0.686	0.687
6	25	0.843	0.851	0.850	0.848

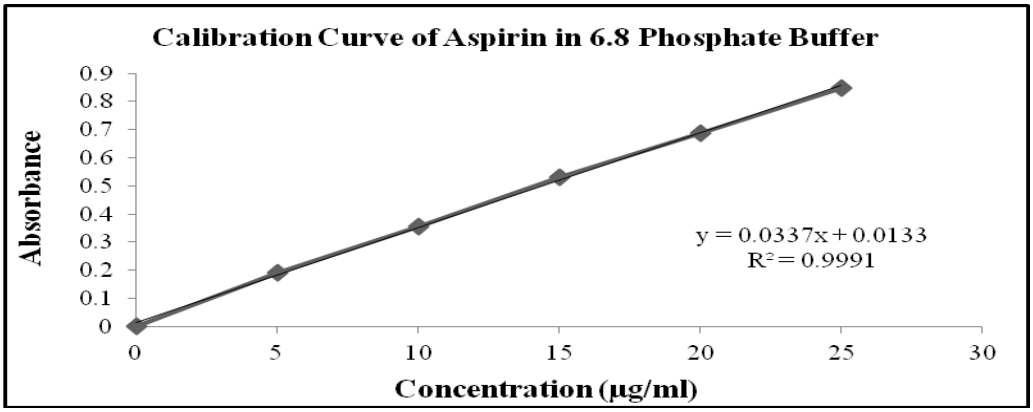

Figure 8: Calibration curve of Aspirin in 6.8 phosphate buffer at 272nm

Solubility Study:

solubility studies were carried out by each adding excess of drug in screw-capped vials each containing 50 ml different solubility medium such as water, 1.2 pH buffer, 3.0 pH buffer, 6.8 pH buffer, 7.4 pH buffer. The suspensions were continuously stirred on electromagnetic stirrer (Remi, India) at 37°C and 300 rpm for three hours. The suspensions were filtered through 0.22 µm membrane filter. The filtrates were suitably diluted and analyzed, spectrophotometrically (Shimazdu-1700, UV/Visible spectrophotometer), for the dissolved drug at 272 nm.

Table 8: Solubility data of Aspirin

Medium	Solubility (mg/50ml)
Distilled Water	247
1.2 pH buffer	216
3.0 pH buffer	189
6.8 pH buffer	231
7.4 pH buffer	237

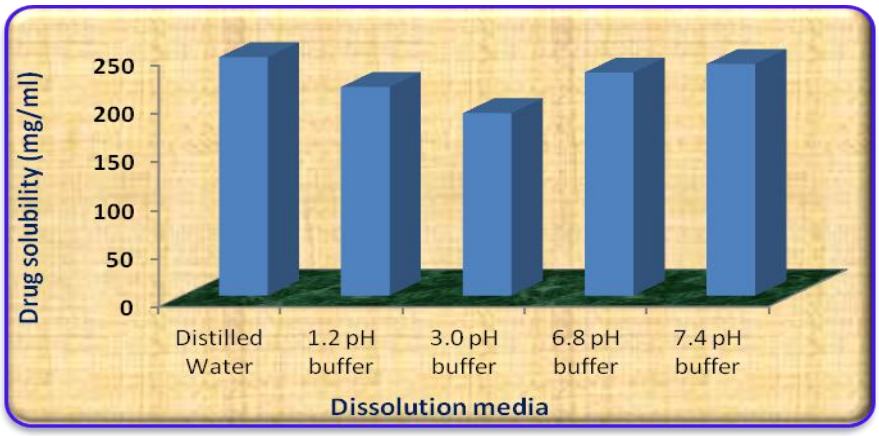

Figure 9: Solubility profile of Aspirin

CONCLUSION:

Acetylsalicylic acid is an analgesic, antipyretic, antirheumatic, and anti-inflammatory agent. Acetylsalicylic acid's mode of action as an anti-inflammatory and antirheumatic agent may be due to inhibition of synthesis and release of prostaglandins. Acetylsalicylic acid appears to produce analgesia by virtue of both a peripheral and CNS effect.

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