2.1 Literature Review

**Arora et al. (2011)** developed oral controlled release mucoadhesive matrix tablets of domperidone as model drug using natural mucoadhesive material myrrh oleo gum resin (MOGR). The tablets were formulated with the natural polymer in different concentrations (5, 10, 15 and 20 % w/w) employing direct compression technology. The prepared batches were evaluated for tablet parametric test (drug assay, diameter, thickness, hardness and tensile strength), swelling index, mucoadhesive strength (using texture analyser) and *in-vitro* drug release studies. Accelerated stability studies were also conducted on all the prepared batches. The tensile strength increased from 0.973±0.09 to 1.687±0.11 MN/m² and mucoadhesive strength from 19.868 to 49.778 N with the increase in natural polymer concentration from 5 to 20 % (M1 to M4). Swelling index of natural polymer was also determined by increasing gum concentration and the time period. The release kinetic and mechanism of release were calculated by fitting *in-vitro* release data in various models demonstrating that release follows zero order and Hixson-Crowell cube root law. The release exponent (n) ranged in between 0.5889 to 0.7389 indicating multiple release mechanisms possibly the combination of diffusion and erosion. Accelerated stability studies demonstrated no significant change in the tensile strength, mucoadhesive strength and drug assay. These research outcomes clearly specify the potential of MOGR to be used as binder, release retardant and mucoadhesive natural material in tablet formulations [1].

**Phani Kumar et al. (2011)**, evaluated tamarind seed polysaccharide (TSP) obtained from the seed kernel of *Tamarindus indica*. It possessed properties like high viscosity mucilage, broad pH tolerance, no carcinogenicity, mucoadhesive nature, and biocompatibility. It is used as stabilizer, thickener, gelling agent, and binder in food and pharmaceutical industries. The objective of investigation was to search for a cheap and effective natural excipient that can be used as an effective alternative for the formulation of pharmaceutical formulations. Thus this mucilage is expected to be a non-toxic, biodegradable, cheap, economic and easily available option as a natural polymer [2].
Prasanthi et al. (2011), investigated the effect of gums namely acacia, tragacanth, guar gum, gum karaya and gum olibanum as binders on the disintegration, dissolution rate and other qualities of Ziprasdone tablets. Based on dissolution rate ($k_1$) and dissolution efficiency (DE60) values the order of performance of binders was gum karaya > acacia > gum olibanum > tragacanth > guar gum. Among all gum karaya and acacia gave significantly higher dissolution rate and DE60. Good correlation ($r = 0.934$) was observed between disintegration times and dissolution characteristics of various tablets [3].

Gowthamarajan et al. (2011), investigated the binding efficacy of cashew nut tree gum in tablet formulation in comparison to standard binders such as acacia and polyvinyl pyrrolidone (PVP K-30). The paracetamol granules were prepared with different concentration of the gum as binder by wet granulation method. The granules were evaluated and found to be satisfactory for preparing compressed tablets. The tablets were prepared from the granules by hydraulic hand press and evaluated for volume of tablet, apparent density, porosity, relative density (or) packing fraction, percentage elastic recovery, tablet physical stability, content uniformity, weight variation, hardness, friability, disintegration time, in-vitro dissolution studies and surface analysis by SEM. Formulations containing the minimum concentration of 2.5% cashew nut tree gum as binding agent show short disintegration and fast dissolution including good physico-mechanical properties. The results suggested that cashew nut tree gum can be used as an alternative binder with 2.5% concentration to produce a tablet of better mechanical strength and dissolution profile of particular drug substance [4].

Chaudhari et al. (2011), evaluated the binding property of Boswellia serrata gum. The gum was isolated from oleo-gum resin of Boswellia serrata Roxb. Physicochemical characteristics of gum were studied. Different formulations of tablets using Boswellia serrata gum were prepared by wet granulation method. Tablets were prepared by using aceclofenac as model drug and evaluated for hardness, friability, drug content uniformity. Preliminary evaluation of granules showed 1.52 to 3.50 % friability, 31.69° to 35.66 ° angles of repose and 5.849 to 7.212 %compressibility index. Tablet hardness was found to be in the range of 2.33 to 4.83 kg/cm², 144 to 252 sec disintegration time and more than 85% dissolution in 105 min. Tablets at 8% w/v binder concentration showed
optimum results. The *Boswellia serrata* gum was found to be useful for the uncoated tablet dosage form [5].

**Kharwade et al. (2011)** formulated mucoadhesive tablets of diclofenac (as a model drug) using *Aegle marmelos* fruit gum as a binder. The preliminary evaluation of *Aegle marmelos* gum showed bulk density 0.42 ± 0.2 g/cm$^3$, tapped density 0.45 ± 0.3 g/cm$^3$ and angle of repose 29$^0$ ± 0.15$^0$. Six tablet formulations were prepared by direct compression. Tablets were evaluated for uniformity of weight, hardness, friability, drug content uniformity, swelling behavior, release rate study, mucoadhesive study, and tensile strength study. Drug additive interaction was also studied using FTIR. The *in-vitro* drug release of F4 formulation exhibited complete release of Diclofenac Sodium with non fickian first order release kinetic. The formulation F4 exhibited tensile strength 0.27 N with 10 hrs of mucoadhesion. From the study it was concluded that the *Aegle marmelos* gum can be used as mucoadhesive sustained release matrix tablet [6].

**Kothari et al. (2011)** investigated the potential of *mucuna* gum as a binder in tablet formulations. The gum was extracted from the seeds, evaluated for relevant properties and used as a binder. Diclofenac was used as a model drug for the study. The prepared tablets were evaluated for general appearance, content uniformity, hardness, friability and disintegration time. Diclofenac tablets containing maize starch as standard binder were produced and assessed. It indicated that *mucuna* gum performs as good as maize starch as a binder to diclofenac tablets. It was concluded that *mucuna* gum (12%) may be used as a binding agent in the conventional tablet formulation [7].

**Shivalingam et al. (2010)** isolated gum from the seed of plant Cassia roxburghii by filtration and hot continuous percolation method then evaluated for its binding properties in the formulation of Paracetamol tablet. The binding properties of gum were evaluated in relation to conventional binder like guar gum, gelatin, sodium CMC at different parameter like percentage of fines, tablet hardness, disintegration time, dissolution and friability and found that 8% binding concentration of both gum shows superior binding properties when compared to the other binders. Further increase in binding concentration of filtered and defatted *C. roxburghii* gum from 8% to 12% showed decrease in
percentage of fines, increase in hardness, increase in disintegration time, decrease in the percentage of friability and decrease in % cumulative release. The binder-excipients interaction study was also carried out by using FTIR i.e. by KBr pellet method which showed that C. roxburghii gum is compatible with drug and all excipients in the formulation. Results indicate that paracetamol tablets prepared with 8 % of mucilage were found to be ideal for the preparation of uncoated tablet formulation [8].

Shivalingam et al. (2010), isolated gum from the stem of Moringa oleifera and studied it for its binding properties in the formulation of conventional paracetamol tablet (500mg). The binding property of gum was evaluated in relation to conventional binder like gelatin at different parameter like percentage of fines, tablet hardness, disintegration time, dissolution and friability. Studies showed that increase in concentration of M. oleifera gum decreases the percentage of fines, increases the hardness, increases the disintegration time, decreases the percentage of friability and decreases % cumulative release. The binder-excipients interaction study was also carried out by using FTIR i.e. by KBr pellet method which showed that M. oleifera gum was compatible with drug and all excipients in the formulation. From the studies it was concluded that increase in binder concentration decreases drug release hence this gum can be used to formulate sustained/controlled release tablet formulation [9].

Adeleye et al. (2010), analyzed the quantitative effects of a new gum as a binder, on the mechanical and release properties of paracetamol tablet formulations in a $2^3$ full factorial experiment. Cissus gum extracted from Cissus populnea Guill. & Perr. (Vitaceae) was compared with official gelatin. The individual and interaction effects of type of binder, concentration of binder and packing fraction on the friability, tensile strength, brittle fracture index, disintegration time and drug release profile of tablets were determined. Changing the binder from gelatin to Cissus gum led to an increase in friability and a decrease in tensile strength, brittle fracture index (BFI) and drug release variables. Increasing binder concentration from 2.0 w/w to 4.0% w/w, and increasing relative density from 0.80 to 0.90, led to increase in lamination tendency and release rate of the formulations. Tablets containing gelatin had higher tensile strength, lower friability, longer disintegration time and a greater tendency to laminate than those with cissus gum.
Hence, care must be taken in choosing a suitable binder for tablet formulations, with respect to their mechanical and release characteristics. The study suggested that cissus gum should be preferred to gelatin in tablet formulations that tend to cap or laminate or in formulations meant for rapid drug release [10].

Patil et al. (2010), formulated the oral tablets of paracetamol by using *Aegle marmelos* fruit gum as a binder. The four different tablet formulations were prepared by wet granulation method. The binder concentrations used in the formulation were 2, 4, 6 and 8% w/v of *A. marmelos* fruit gum, tablets were evaluated for hardness, friability, drug content uniformity. Preliminary evaluation of granules showed 0.71 to 0.77 mm granule size, 29.20 to 30.10° angles of repose and 22.1 to 12.7% fines. Hardness was found in the range of 7.1 to 7.4 kg cm\(^{-2}\), the percent friability was in the range of 1.50 to 0.75%. The tablet contained 97.46 to 98.96% of labeled amount of paracetamol indicating uniformity in drug content, 8 to 18 min disintegration time and more than 90% dissolution in 75 min. Tablets at 6% w/w binder concentration showed optimum results. The *Aegle marmelos* gum was found to be useful for the preparation of uncoated tablet dosage form [11].

Selvi et al. (2010), isolated hydrophilic mucilage from the seeds of *Prosopis juliflora* (Mimosaceae) and studied the potential of mucilage in tablet formulation as a binder. The DSC thermogram of the drug, drug-mucilage mixture indicated no chemical interactions. The different tablet formulations of *Prosopis juliflora* mucilage were prepared using lactose as diluent, diclofenac sodium as a model drug and 2% of talc and magnesium stearate were used as a glidant and lubricant respectively. The granules were prepared by wet granulation technique and evaluated for properties like flow rate, Carr index, Hausner ratio and angle of repose and was compared with starch which was used as standard binder. The tablets were compressed and evaluated for various parameters like weight variation, hardness, friability, disintegration and *in-vitro* dissolution. The results obtained showed that the granules have the excellent flow property and the tablets prepared using 8 and 10 % of mucilage showed drug release over a period of 5 h and exhibited more hardness than other formulations [12].
Dinda et al. (2009), reported that the fruit mucilage obtained from *cordia obliqua* can be used as pharmaceutical excipient in particular as tablet binder and emulsifier. Gum cordia at a very low amount (1/25th of the starch paste used) was found to be effective as tablet binder. For emulsifying activity study, castor oil was taken as a model drug and emulsified with *cordia obliqua* fruit mucilage. The comparative stability studies were done with that of the emulsion prepared by taking gum acacia as standard emulsifying agent and it was found that the emulsion prepared with 1.5%w/v of gum cordia was more effective in comparison to that of the emulsion prepared by using 10%w/v of gum acacia[13].

Patil et al. (2009), formulated oral tablets of paracetamol by using cordial fruit gum as a binder. Four different tablet formulations were prepared by wet granulation method. The evaluation of granules showed 0.643 to 0.746 mm granule size, 26.65 to 32.10° angles of repose and 21.8 to 13.4 % fines. Tablets were compressed to hardness of about 7.5 to 8.2 kg/cm². The evaluation of tablet exhibited 1.58 to 1.10 % friability, 12 to 22 min disintegration time and more than 90 % dissolution in 75 min. Tablets at 6 % w/w binder concentration showed optimum results as tablet binder. The cordial fruit gum was found to be useful for the preparation of uncoated tablet [14]

Girhepunje et al. (2009), evaluated *Cassia roxburghii* seed gum for its binding property. The isolated gum was evaluated for its binding property on the basis of % of fines, stability and viscosity. The adhesive and cohesive properties of the tablet like hardness, friability, disintegration time and dissolution rate were evaluated on paracetamol tablets. All evaluations were compared with widely used standard sodium carboxy methyl cellulose and gelatin. The gum was isolated from seeds of *Cassia roxburghii* and the isolated gum was evaluated in different concentration like 1%, 1.5% and 2% which was further compared with the same concentration of sodium CMC and gelatin. The *Cassia roxburghii* seed gum was found to be more viscous than sodium CMC and gelatin. Only the marginal difference was found in the hardness of tablet when compared with standard sodium CMC and gelatin. It also showed linearity between concentration and hardness. Increased concentration of *Cassia roxburghii* seed gum from 2 to 6% increased the disintegration and dissolution time. Cassia roxburghii gum produce tablet with better
mechanical property, longer disintegration and dissolution time than those containing sodium CMC and gelatin. The study suggested that *Cassia roxburghii* gum could be a useful binding agent especially when high mechanical strength and slower release is of concern [15].

**Adetogun et al. (2009)** studied the mechanical and disintegration properties of paracetamol tablets formulated using *Delonix regia* seed gum (DRSG) as a binder. Acacia BP (ACG) and tragacanth BP (TRG) were used as official gum standards. The mechanical properties, i.e. tensile strength (TS) and brittle fracture index (BFI), showed that with an increase in concentration of the gum binder, the tensile strength increased while the BFI was reduced. The crushing strength and friability/disintegration time ratio used to analyze the disintegration properties gave a rank order: tablets containing DRSG > tablets containing ACG > tablets containing TRG at 1%, w/w binder concentration while for higher binder concentrations, the rank order was: tablets containing ACG > tablets containing TRG > tablets containing DRSG. The results suggested that *Delonix regia* seed gum may be useful as a binder. Its use at a low concentration will improve the balance between the binding and disintegration properties of tablets when a faster disintegration is desired, while its use at a high concentration could serve the desire for a modified or sustained release tablet formulation [16].

**Kale et al. (2009)** evaluated the seeds of *Delonix regia* plant which contain glucomannose for suitability as tablet binder. Seeds collected from dried pods of *D. regia* were used for preparation of mucilage. The mucilage obtained was used for preparation of calcium carbonate tablets (formulation B). The tablets were evaluated for hardness test, friability and disintegration time and results were compared with standard calcium carbonate tablets (formulation A) prepared using 5%w/v starch paste as binding agent. Hardness of test formulation was found to be 6.0 kg/cm³, the friability was just 0.26% and the disintegration time was 7 min. The properties were compared with standard formulation A. The results indicated that endospermic mucilage obtained from *D. regia* seeds possesses comparable binding properties [17].
Panda et al. (2008), undertaken a study to find out the potential of gum from Moringa oleifera that could act as a binder and release retardant in tablet formulations. The effect of calcium sulphate dihydrate (water insoluble) and lactose (water soluble) diluent on the release of propranolol hydrochloride was studied. The DSC thermograms of drug, gum and mixture of gum/drug indicated no chemical interaction. Tablets were prepared containing calcium sulphate dihydrate as diluent, propranolol hydrochloride as model drug using 10%, 8%, 6% and 4% w/v of gum solution as binder. Magnesium stearate was used as lubricant. Physical and technological properties of granules and tablets like flow rate, Carr index, Hausner ratio, angle of repose, hardness, friability and disintegration time were determined and found to be satisfactory. Tablets were prepared by wet granulation method containing calcium sulphate dihydrate as excipient, propranolol hydrochloride as model drug using 10%, 20% and 30% of gum as release retardant, magnesium stearate was used as lubricant. Similarly tablets were prepared replacing lactose with calcium sulphate dihydrate. Despite of the widely varying physico-chemical characteristics of the excipients, the drug release profiles were found to be similar. The drug release increased with increasing proportions of the excipient and decreased proportion of the gum irrespective of the solubility characteristics of the excipient. The values of release exponent ‘n’ were between 0.37 and 0.54. This implies that the release mechanism is Fickian. There was no evidence that the dissolution or erosion of the excipient has got any effect on the release of the drug. The t_50% values for tablets containing calcium sulphate dihydrate were on an average 10%-15% longer than the tablets containing lactose as excipient. These relatively small differences in t_50% values suggested that the nature of excipient used appeared to play a minor role in regulating the release, while the gum content was a major factor [18].

Eichie et al. (2007) carried out a comparative study to investigate the binder effects of the gums of Cissus populnea and Accasia senegal on the mechanical properties of paracetamol tablets. Tablet mechanical properties like packing fraction (Pf), the tensile strength (T) and the brittle fracture tendency (BFI) were evaluated. Varying concentrations of the gum mucilage ranging from 1 - 15% (w/v) were prepared and their relative viscosities were determined. At all binder concentrations A. senegal gum
produced harder and more consolidated tablets than *C. populnea* as reflected by the higher T and P values respectively. For instance, the T and P values of the tablets at binder concentration of 10% (w/v) were 0.69 MNm$^{-2}$ and 0.47 (*A. senegal*) and 0.57 MNm$^{-2}$ and 0.23 (*C. populnea*), respectively. On the contrary, an increase in binder concentration generally resulted in a decrease in BFI values and this decrease was more marked with *C. populnea*. The study showed that *A. senegal* mucilage display better tableting characteristics and higher tendency for ameliorating capping tendency. Both mucilages have the potentials for substitution as binder for the more expensive starches in tablet formulation [19].

**Mukherjee et al. (2006)**, investigated the efficacy of gum odina as tablet excipient, particularly as a tablet binder. The studies of toxicity and chemical composition of the experimental gum and gum-experimental tablet excipient interactions using FTIR spectrum ensured its safe use as a tablet binder. Tablets were manufactured with various quantities of gum odina as a tablet binding agent and a comparison was made against the tablets prepared with 5% starch paste as binder based on studying the standard parameters like hardness, thickness, friability, weight variation and disintegration time. Gum odina at a very low amount (1/20th of the starch paste used) was found to be effective as tablet binder. Thus this gum is a cheap, economic and easily available option of a tablet binder in the list of pharmaceutical excipients [20].

**Tavakoli et al. (2004)**, evaluated the effectiveness of a new binder extracted from *Hibiscus esculentus* (Okra gum) in tablet formulation. *Hibiscus esculentus* gum was extracted from the pods of okra fruit by maceration in distilled water followed by filtration of viscous solution as well as precipitation of gum extract by using acetone. To evaluate the binder effectiveness, two models including a placebo formulation (lactose) and a drug formulation (acetaminophen, ibuprofen, and/or calcium acetate) were evaluated. Granules were prepared by different concentrations (0.5-6%) of Okra gum and tablets were made using a Kilian single punch press. Cornstarch (12.5%) and P.V.P (2%) were employed as the standard binders for comparison. The physical properties of the granules and those of the tablets including disintegration time and dissolution rate were studied. The dissolution studies of tablets were performed in order to evaluate the role of
binder in drug release in comparison with common binders. The properties of placebo granulate (bulk and tapped density, granule strength, flowability) as well as those of tablets (hardness, friability, disintegration time) were generally good. However the physical properties of ibuprofen and calcium acetate tablets containing Okra gum showed sufficient hardness (breaking load 55 N and 59.3 N), slow disintegration (completed after 35 min and 24 min) and low friability. The results showed that the drug release from tablets containing Okra gum significantly decreased (p<0.05) in comparison with other binders. Hibiscus esculentus gum produces some tablet formulations with good hardness and friability. However this binder prolongs the dissolution rate and hence may be good candidate for sustain release formulations [21].

Odeku et al. (1998), performed a study of the comparative effects of khaya gum and two standard binding agents, polyvinylpyrrolidone (PVP) and gelatin, on the compressional characteristics of a paracetamol tablet formulation and on the mechanical properties of the tablets. Compressional characteristics were analysed using density measurements and the Heckel and Kawakita plots. The loose initial relative density (D₇₀) of the formulation increased with increased binder concentration while the packed initial relative density (D₈₀) decreased. The degree of densification achieved for the formulation at low pressures (D₇₀) and at both zero and low pressures (D₈₀) decreased with increased binder concentration. The mean yield pressure (Pₚ) for the formulation decreased with increase in binder concentration, with formulations containing khaya gum having the lowest Pₚ values and those containing gelatin exhibiting the highest values. Another pressure term, Pₖ (an inverse measure of plasticity) decreased with increase in binder concentration, with formulations containing PVP having the lowest Pₖ values and those containing khaya gum and gelatin having similar Pₖ values. The tensile strength (T) of the paracetamol tablets increased with increase in binder concentration while the brittle fracture index (BFI) decreased. Tablets containing PVP exhibited the highest T values while those containing khaya gums exhibited the lowest values. The same trend was obtained for the BFI values with tablets containing khaya gum exhibiting the lowest values [22].
2.2 Research envisaged

Pharmaceutical binders are materials added dry or in liquid form to form granules or to promote cohesive compacts for directly compressed tablets. These include natural gums, alginic and alginites, starches, liquid glucose, cellulose derivatives and polyvinylpyrrolidone. Natural gums like acacia and tragacanth are employed in solutions ranging from 10-25% concentration alone or in combination.

Together with neighbouring countries, India due to its diverse agro-climatic conditions has remained the natural home of various species of natural gums since time immemorial. Gum olibanum (from *Boswellia spp*.), gum myrrh (from *Commiphora spp*.), gum karaya (from *Sterculia spp*.) and gum acacia (from *A. senegal* and *A. seyal spp*.) are reported to yield gum and resin products of commercial value.

More than 40 species of the genus acacia have been explored but *A. senegal*, *A. seyal*, *A. polyacantha* (Gumo) and *A. drepanolobium* are the four species reported to yield economically important gums. Almost 100 percent of the existing gum and resin bearing trees under consideration are naturally and wildly grown under arid, warm or hot, very sloppy and rugged topographic conditions in almost all regions. The plants selected for present study are important agro and social forestry trees. Also, these plants contain gums/mucilages of medicinal and social uses. However, no work has been reported so far on these plants for exploring the potential of their gums as tablet binder. Therefore, the present study was carried out to investigate the binding efficiency of local gums obtained from the plants found in Garhwal region of Himalayas in India in tablet formulation. The study included following plants.

- *Grewia optiva*
- *Myrica*
- *Bombax ceiba*
- *Aesculus indica*
- *Prunus persica*
The gums obtained from the above plants were evaluated for their potential as tablet binder using two model drugs; paracetamol, which is both sparingly soluble and poorly compressible drug, and diclofenac sodium, which is a freely soluble drug.

### 2.3 Plan of work

The work was carried out on the following lines:

1. Selection of the plants
2. Extraction and purification of the gums from the selected plants
3. Characterization of gums
4. Determination of rheological properties of the gums
5. Preparation of granules using selected gums and their evaluation for
   a. Size and size distribution
   b. Bulk density, tapped density and granule density
   c. Compressibility
   d. Granule friability
   e. Flowability
6. Preparation and optimization of tablets and their evaluation for
   a. Hardness
   b. Friability
   c. Porosity
   d. Disintegration time
   e. Dissolution rate
   f. Brittle fracture Index (BFI)
7. Compilation of the data and submission of the thesis
2.4 References


